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(54) Title: DIAGNOSIS AND TREATMENT OF VASCULAR DISEASE

(57) Abstract: The present invention is based at least in part on the discovery of polymorphisms within the phospholipase C gamma 1 (PLCG1) gene and the plasminogen activator inhibitor type 2 (PAI-2) gene. Accordingly, the invention provides nucleic acid molecules having a nucleotide sequence of an allelic variant of a PLCG1 or PAI-2 gene. The invention also provides methods for identifying specific alleles of polymorphic regions of a PLCG1 or PAI-2 gene, methods for determining whether a subject is or is not at risk of developing a disease which is associated with a specific allele of a polymorphic region of a PLCG1 or PAI-2 gene, *e.g.*, a vascular disease, based on detection of polymorphisms within the PLCG1 or PAI-2 gene, and kits for performing such methods. The invention further provides methods for classifying a subject who is or is not at risk for developing, a vascular disease or disorder as a candidate for a particular clinical course of therapy or a particular diagnostic evaluation. The invention further provides methods for selecting a clinical course of therapy or a diagnostic evaluation to treat a subject who is or not at risk for developing, a vascular disease or disorder.

Diagnosis and Treatment of Vascular Disease

Related Applications

This application claims priority to U.S. Patent Application No. 10/017,128, filed December 14, 2001 (pending), which claims priority to U.S. Provisional Application Serial No. 60/306,941, filed on July 20, 2001, to U.S. Provisional Application Serial No. 60/315,572, filed on August 28, 2001, and to U.S. Provisional Application Serial No. 60/327,488, filed on October 5, 2001, the contents of which are incorporated herein in their entirety by reference.

Background of the Invention

Cardiovascular disease is a major health risk throughout the industrialized world. Coronary artery disease (CAD), or atherosclerosis, involves the progressional narrowing of the arteries due to a build-up of atherosclerotic plaque. Myocardial infarction (MI), *e.g.*, heart attack, results when the heart is damaged due to reduced blood flow to the heart caused by the build-up of plaque in the coronary arteries.

Coronary artery disease, the most prevalent of cardiovascular diseases, is the principal cause of heart attack, stroke, and gangrene of the extremities, and thereby the principle cause of death in the United States. Coronary artery disease, or atherosclerosis, is a complex disease involving many cell types and molecular factors (described in, for example, Ross, 1993, *Nature* 362: 801-809). The process, in normal circumstances a protective response to insults to the endothelium and smooth muscle cells (SMCs) of the wall of the artery, consists of the formation of fibrofatty and fibrous lesions or plaques, preceded and accompanied by inflammation. The advanced lesions of atherosclerosis may occlude the artery concerned, and result from an excessive inflammatory-fibroproliferative response to numerous different forms of insult. Injury or dysfunction of the vascular endothelium is a common feature of may conditions that predispose a subject to accelerated development of atherosclerotic cardiovascular disease. For example, shear stresses are thought to be responsible for the frequent occurrence of

atherosclerotic plaques in regions of the circulatory system where turbulent blood flow occurs, such as branch points and irregular structures.

The first observable event in the formation of an atherosclerotic plaque occurs when blood-borne monocytes adhere to the vascular endothelial layer and transmigrate through to the sub-endothelial space. Adjacent endothelial cells at the same time produce oxidized low density lipoprotein (LDL). These oxidized LDLs are then taken up in large amounts by the monocytes through scavenger receptors expressed on their surfaces. In contrast to the regulated pathway by which native LDL (nLDL) is taken up by nLDL specific receptors, the scavenger pathway of uptake is not regulated by the monocytes.

These lipid-filled monocytes are called foam cells, and are the major constituent of the fatty streak. Interactions between foam cells and the endothelial and SMCs which surround them lead to a state of chronic local inflammation which can eventually lead to smooth muscle cell proliferation and migration, and the formation of a fibrous plaque.

Such plaques occlude the blood vessel concerned and, thus, restrict the flow of blood, resulting in ischemia. Ischemia is a condition characterized by a lack of oxygen supply in tissues of organs due to inadequate perfusion. Such inadequate perfusion can have a number of natural causes, including atherosclerotic or restenotic lesions, anemia, or stroke. Many medical interventions, such as the interruption of the flow of blood during bypass surgery, for example, also lead to ischemia. In addition to sometimes being caused by diseased cardiovascular tissue, ischemia may sometimes affect cardiovascular tissue, such as in ischemic heart disease. Ischemia may occur in any organ, however, that is suffering a lack of oxygen supply.

One of the most important risk factors for coronary artery disease is a familial history. Although family history subsumes both genetic and shared environmental factors, studies suggest that CAD has a very strong genetic component (Marenberg, *et al.* (1994) *NEJM* 330:1041). Despite the importance of family history as a risk factor for CAD, it's incomplete genetic basis has not been elucidated. Therefore, the identification of genes which are involved in the development of CAD and MI would be beneficial.

The phospholipase C gamma 1 gene (PLCG1) hydrolyzes phosphatidylinositol 4,5-bisphosphate to generate the second messengers, inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 induces a transient increase in intracellular free Ca2+, while DAG directly activates protein kinase C. Upon stimulation of cells with growth factors, PLCG1 is activated upon their association with and phosphorylation by receptor and non-receptor tyrosine kinases as well as interaction with specialized adaptor molecules and, perhaps, other second messenger molecules (Kim, *et al.* (2000) *Exp. Mol. Med.* 30;32(3):101-9 and Carpenter, *et al.* (1999) *Exp Cell Res* 253(1):15-24). It has been found that the specific binding of phosphatidic acid to PLCG1 is decreased in an experimental animal model of the failing heart (Tappia, *et al.* (2001) *J. Mol. Cell* 33(3):431-40).

Plasminogen activator inhibitor type 2 (PAI-2) is an important regulator of plasminogen activation which is involved in the regulation of vascular remodeling, maintenance of intervillous blood flow, and in the regulation of cell migration and proliferation (Irigoyen, *et al.* (1999) *Cell Mol Life* 56(1-2):104). PAI-2 has also been identified as playing a role in the inflammatory process (Kruithof, E. (1997) *Hematologie* 3:7-12).

It would thus be beneficial to identify polymorphic regions within the PLCG1 and PAI-2 genes which are associated with a vascular disease or disorder, such as coronary artery disease or myocardial infarction. It would further be desirable to provide prognostic, diagnostic, pharmacogenomic, and therapeutic methods utilizing the identified polymorphic regions.

Summary of the Invention

The present invention is based, at least in part, on the identification of polymorphic regions within the phospholipase C gamma 1 gene (PLCG1) and the plasminogen activator inhibitor type 2 gene (PAI-2), which are associated with specific diseases or disorders, including vascular diseases or disorders. In particular, single

nucleotide polymorphisms (SNPs) in these genes which are associated with premature coronary artery disease (CAD) (or coronary heart disease) and myocardial infarction (MI) have been identified.

The present invention is based, also in part, on the discovery that a subject having two copies of the variant allele of the PLCG1 gene (TT) at residue 64001 of the reference sequence GI 11345540 and two copies of the reference allele of the PAI-2 gene (AA) at residue 170871 of the reference sequence GI 6705901, in combination, is at a decreased risk of developing a vascular disease such as CAD or MI compared to a subject having any other possible combination of alleles at these residues. Thus, the invention relates to polymorphic regions and in particular, SNPs identified as described herein, both singly and, preferably, in combination, as well as to the use of these SNPs, and others in these genes, particularly those nearby in linkage disequilibrium with these SNPs, both singly and, preferably, in combination, for predicting the risk of developing a vascular disease or disorder such as CAD and MI in a subject.

The SNPs identified herein may further be used in the development of new treatments for vascular disease based upon comparison of the variant and normal versions of the gene or gene product (*e.g.,* the reference sequence), and development of cell-culture based and animal models for research and treatment of vascular disease. The invention further relates to novel compounds and pharmaceutical compositions for use in the diagnosis and treatment of such disorders. In preferred embodiments, the vascular disease is CAD or MI.

The polymorphisms of the invention may thus be used, both singly, or, preferably, in combination, in prognostic, diagnostic, and therapeutic methods. For example, the polymorphisms of the invention can be used to determine whether a subject is or is not at risk of developing a disease or disorder associated with a specific allelic variant of a PLCG1 or PAI-2 polymorphic region, *e.g.,* a disease or disorder associated with aberrant PLCG1 or PAI-2 activity, *e.g.*, a vascular disease or disorder such as CAD or MI.

The invention thus relates to isolated nucleic acid molecules and methods of using these molecules. The nucleic acid molecules of the invention include specific PLCG1 or PAI-2 allelic variants which differ from the reference PLCG1 or PAI-2 sequences set forth in SEQ ID NO:1 (GI 11345540) or SEQ ID NO:3 (GI 6705901), respectively, or a portion thereof. The preferred nucleic acid molecules of the invention comprise PLCG1 or PAI-2 polymorphic regions or portions thereof having the polymorphisms shown in Table 3 (corresponding to SEQ ID NOs:5 and SEQ ID NO:6), polymorphisms in linkage disequilibrium with the polymorphisms shown in Table 3, and combinations thereof. Nucleic acids of the invention can function as probes or primers, *e.g.*, in methods for determining the allelic identity of a PLCG1 or PAI-2 polymorphic region in a nucleic acid of interest.

The nucleic acids of the invention can also be used, singly, or, preferably, in combination, to determine whether a subject is or is not at risk of developing a disease associated with a specific allelic variant of a PLCG1 or PAI-2 polymorphic region, *e.g.*, a disease or disorder associated with aberrant PLCG1 or PAI-2 activity, *e.g.*, a vascular disease or disorder such as CAD or MI. The nucleic acids of the invention can further be used to prepare PLCG1 or PAI-2 polypeptides encoded by specific alleles, such as mutant (variant) alleles. Such polypeptides can be used in therapy. Polypeptides encoded by specific PLCG1 or PAI-2 alleles, such as variant PLCG1 or PAI-2 polypeptides, can also be used as immunogens and selection agents for preparing, isolating or identifying antibodies that specifically bind PLCG1 or PAI-2 proteins encoded by these alleles. Accordingly, such antibodies can be used to detect variant PLCG1 or PAI-2 proteins.

There are two preferred polymorphisms of the invention. One polymorphism found in the population screened is a change from a cytidine (C) to a thymidine (T) in the PLCG1 gene at residue 64001 of the reference sequence GI 11345540 or a change from a C to a T at residue 4363659 of the reference sequence GI 13653753 (polymorphism ID No. G329u1). This polymorphism results in a change from an isoleucine to a threonine in the amino acid sequence of PLCG1 (SEQ ID NO:2) at amino acid residue 813. A

second polymorphism is a change from a thymidine (T) to a cytidine (G) at residue 170871 of the reference sequence GI 6705901 (polymorphism ID No. PAI2u1). This polymorphism results in a change from an asparagine to an aspartic acid in the amino acid sequence of PAI-2 (SEQ ID NO:4) at amino acid residue 120.

The nucleic acid molecules of the invention can be double- or single-stranded. Accordingly, in one embodiment of the invention, a complement of the nucleotide sequence is provided wherein the polymorphism has been identified. For example, where there has been a single nucleotide change from a thymidine to a cytidine in a single strand, the complement of that strand will contain a change from an adenine to a guanine at the corresponding nucleotide residue. The invention further provides allele-specific oligonucleotides that hybridize to a gene comprising a polymorphism of the present invention or to its complement.

The polymorphisms of the present invention, either singly, in combination with each other, or in combination with previously identified polymorphisms, are shown herein to be associated with specific disorders, *e.g.*, vascular diseases or disorders. Examples of vascular diseases or disorders include, without limitation, atherosclerosis, coronary artery disease (CAD), myocardial infarction (MI), ischemia, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism.

The invention further provides vectors comprising the nucleic acid molecules of the present invention; host cells transfected with said vectors whether prokaryotic or eukaryotic; and transgenic non-human animals which contain a heterologous form of a functional or non-functional PLCG1 or PAI-2 allele described herein. Such a transgenic animal can serve as an animal model for studying the effect of specific PLCG1 or PAI-2 allelic variations, including mutations, as well as for use in drug screening and/or recombinant protein production.

In another preferred embodiment, the method comprises determining the nucleotide content of at least a portion of a PLCG1 or PAI-2 gene, such as by sequence analysis. In yet another embodiment, determining the molecular structure of at least a portion of a PLCG1 or PAI-2 gene is carried out by single-stranded conformation

polymorphism (SSCP). In yet another embodiment, the method is an oligonucleotide ligation assay (OLA). Other methods within the scope of the invention for determining the molecular structure of at least a portion of a PLCG1 or PAI-2 gene include hybridization of allele-specific oligonucleotides, sequence specific amplification, primer specific extension, and denaturing high performance liquid chromatography (DHPLC). In at least some of the methods of the invention, the probe or primer is allele specific. Preferred probes or primers are single stranded nucleic acids, which optionally are labeled.

The methods of the invention can be used for determining the identity of a nucleotide or amino acid residue within a polymorphic region of a human PLCG1 or PAI-2 gene present in a subject. For example, the methods of the invention can be useful for determining whether a subject is or is not at risk of developing a disease or condition associated with a specific allelic variant of a polymorphic region in the human PLCG1 or PAI-2 gene, *e.g.*, a vascular disease or disorder.

In one embodiment, the disease or condition is characterized by an aberrant PLCG1 or PAI-2 activity, such as aberrant PLCG1 or PAI-2 protein level, which can result from aberrant expression of a PLCG1 or PAI-2 gene. The disease or condition can be CAD, MI, or another vascular disease. Accordingly, the invention provides methods for predicting a subject's risk for developing a vascular disease associated with aberrant PLCG1 or PAI-2 activity. In a preferred embodiment, a subject having two copies of the variant allele of the PLCG1 gene (TT) at residue 64001 of the reference sequence GI 11345540 and two copies of the reference allele of the PAI-2 gene (TT) at residue 170871 of the reference sequence GI 6705901, in combination, is approximately 3-fold less likely to develop a vascular disease such as CAD or MI compared to a subject having any other possible combination of alleles at these residues (see Example 2).

Additionally, the invention provides a method of identifying a subject who is or is not susceptible to a vascular disorder, which method comprises the steps of i) providing a nucleic acid sample from a subject; and ii) detecting in the nucleic acid sample the presence or absence of a PLCG1 or PAI-2 gene polymorphism, or both in

combination, that correlate with the vascular disorder with a P value less than or equal to 0.05.

The invention further provides forensic methods based on detection of polymorphisms within the PLCG1 or PAI-2 gene.

The invention also provides probes and primers comprising oligonucleotides, which correspond to a region of nucleotide sequence which hybridizes to at least 6 consecutive nucleotides of the sequence set forth as SEQ ID NOs:5 and 6 or to the complement of the sequences set forth as SEQ ID NOs:5 and 6, or naturally occurring mutants or variants thereof. In preferred embodiments, the probe/primer further includes a label attached thereto, which is capable of being detected.

A kit of the invention can be used, *e.g.*, for determining whether a subject is or is not at risk of developing a disease associated with a specific allelic variant of a polymorphic region of a PLCG1 or PAI-2 gene, *e.g.*, CAD or MI. In a preferred embodiment, the invention provides a kit for determining whether a subject is or is not at risk of developing a vascular disease such as, for example, atherosclerosis, CAD, MI, ischemia, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism. The kit of the invention can also be used in selecting the appropriate clinical course of clinical treatment to a subject to treat a disease or condition, such as a disease or condition set forth above. Thus, determining the allelic variants of PLCG1 or PAI-2 polymorphic regions of a subject can be useful in predicting how a subject will respond to a specific drug, *e.g.*, a drug for treating a disease or disorder associated with aberrant PLCG1 or PAI-2, *e.g.*, a vascular disease or disorder.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

Brief Description of the Figures

Figure 1 depicts the nucleotide sequence corresponding to reference sequence GI 11345540 (SEQ ID NO:1) for the PLCG gene.

Figure 2 depicts the reference amino acid sequence for the PLCG1 protein (SEQ ID NO:2).

Figure 3 depicts the nucleotide sequence corresponding to reference sequence GI 6705901 (SEQ ID NO:3) for the PA1-2 gene.

Figure 4 depicts the reference amino acid sequence for the PAI-2 protein (SEQ ID NO:4).

Figure 5 is a Table listing the demographic characteristics of cases and controls used in the identification of SNPs associated with vascular disease.

Detailed Description of the Invention

The present invention is based, in part, on the identification of polymorphic regions within the phospholipase C gamma 1 gene (PLCG1) and the plasminogen activator inhibitor type 2 gene (PAI-2). The polymorphic regions of the invention contain polymorphisms which correlate with specific diseases or conditions, including vascular diseases or disorders, including, but not limited to, atherosclerosis, coronary artery disease (CAD), myocardial infarction (MI), ischemia, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism.

The polymorphisms of the present invention are single nucleotide polymorphisms (SNPs) at a specific nucleotide residue within the PLGC1 gene and the PAI-2 gene. The PLGC1 gene and the PAI-2 gene have at least two alleles, referred to herein as the reference allele and the variant allele. The reference alleles (*i.e.*, the consensus sequences) have been designated based on their frequency in a general United States Caucasian population sample. The reference allele is the more common of the two alleles; the variant allele is the more rare of the two alleles. Nucleotide sequences in GenBank may correspond to either allele and correspond to the nucleotide sequence of the nucleotide sequence which has been deposited in GenBank™ and given a specific

Accession Number (*e.g.*, GI 11345540, the reference sequence for the PLCG1 gene or GI 6705901, the reference sequence for the PAI-2 gene, corresponding to SEQ ID NO:1 and SEQ ID NO:3, respectively). The reference sequence for the amino acid sequences of PLCG1 and PAI-2 proteins are set forth as SEQ ID NO:2 and SEQ ID NO:4, respectively. The variant allele differs from the reference allele by at least one nucleotide at the site(s) identified in Table 3 (see Example 1, below), and those in linkage disequilibrium therewith. The present invention thus relates to nucleotides comprising variant alleles of the PLCG1 reference sequence, variant alleles of the PAI-2 reference sequence, and/or complements of the variant alleles to be used singly, or, preferably, in combination.

The invention further relates to nucleotides comprising portions of the variant alleles and/or portions of complements of the variant alleles which comprise the site of the polymorphism and are at least 5 nucleotides or basepairs in length. Portions can be, for example, 5-10, 5-15, 10-20, 2-25, 10-30, 10-50 or 10-100 bases or basepairs long. For example, a portion of a variant allele which is 17 nucleotides or basepairs in length includes the polymorphism (*i.e.*, the nucleotide(s) which differ from the reference allele at that site) and twenty additional nucleotides or basepairs which flank the site in the variant allele. These additional nucleotides and basepairs can be on one or both sides of the polymorphism. Polymorphisms which are the subject of this invention are defined in Table 3 with respect to the reference sequences identified in Table 3 (GI 11345540 or GI 6705901), and those polymorphisms in linkage disequilibrium with the polymorphisms of Table 3. For example, the invention relates to nucleotides comprising a portion of the PLCG1 gene having a nucleotide sequence of GI 11345540 (SEQ ID NO:1), or a portion thereof, comprising a polymorphism at a specific nucleotide residue (*e.g.*, a thymidine at residue 64001, or the complement thereof) and nucleotides comprising a portion of the PAI-2 gene having a nucleotide sequence of GI 6705901 (SEQ ID NO:3), or a portion thereof, comprising a polymorphism at a specific nucleotide residue (*e.g.*, a cytidine at residue 170871, or the complement thereof).

Specific reference nucleotide (SEQ ID NO:1) and amino acid (SEQ ID NO: 2) sequences for PLCG1 are shown in Figures 1 and 2, respectively. Specific reference nucleotide (SEQ ID NO: 3) and amino acid (SEQ ID NO: 4) sequences for PAI-2 are shown in Figures 3 and 4, respectively. It is understood that the invention is not limited by these exemplified reference sequences, as variants of these sequences which differ at locations other than the SNP sites identified herein can also be utilized. The skilled artisan can readily determine the SNP sites in these other reference sequences which correspond to the SNP sites identified herein by aligning the sequence of interest with the reference sequences specifically disclosed herein. Programs for performing such alignments are commercially available. For example, the ALIGN program in the GCG software package can be used, utilizing a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4, for example.

The polymorphic region of the present invention is associated with specific diseases or disorders and has been identified in the human PLCG1 and PAI-2 genes by analyzing the DNA of cell lines derived from an ethnically diverse population by methods described in Cargill, *et al.* (1999) *Nature Genetics* 22:231-238.

Cases which were used to identify associations between vascular disease and SNPs were comprised of 352 U.S. Caucasian subjects with premature coronary artery disease were identified in 15 participating medical centers, fulfilling the criteria of either myocardial infarction, surgical or percutaneous revascularization, or a significant coronary artery lesion diagnosed before age 45 in men or age 50 in women and having a living sibling who met the same criteria. These cases were compared with a random sample of 418 Caucasian controls drawn from the general U.S. population in Atlanta, Georgia. It was determined that a subject having two copies of the variant allele of the PLCG1 gene (TT) at residue 64001 of the reference sequence GI 11345540 and two copies of the reference allele of the PAI-2 gene (TT) at residue 170871 of the reference sequence GI 6705901, or the complements thereof, in combination, is approximately 3-fold less likely to develop a vascular disease such as CAD or MI compared to a subject having any other possible combination of alleles at these residues.

The allelic variants of the present invention were identified by performing denaturing high performance liquid chromatography (DHPLC) analysis, variant detector arrays (Affymetrix™), the polymerase chain reaction (PCR), and/or single stranded conformation polymorphism (SSCP) analysis of genomic DNA from independent individuals as described in the Examples, using PCR primers complementary to intronic sequences surrounding each of the exons, 3' UTR, and 5' upstream regulatory element sequences of the PLCG1 and PAI-2 genes.

The presence of at least one polymorphism in the human PLCG1 gene and one polymorphism in the PAI-2 gene in the population studied were identified. Both of the variants are characterized as single nucleotide polymorphisms (SNPs). The preferred polymorphisms of the invention are listed in Table 3.

Table 3 contains a "polymorphism ID No." in column 2, which is used herein to identify each individual variant. In Table 3, the nucleotide sequence flanking each polymorphism is provided in column 9, wherein the polymorphic residue(s), having the variant nucleotide, is indicated in lower-case letters. There are 8 nucleotides flanking the polymorphic nucleotide residue (*i.e.*, 8 nucleotides 5' of the polymorphism and 8 nucleotides 3' of the polymorphism). Column 10 indicates the SEQ ID NO. that is used to identify each polymorphism. SEQ ID NOs:5 and 6 comprise sequences shown in column 9 with the variant nucleotide at the residue(s) shown by a lower-case letter.

Each polymorphism is identified based on a change in the nucleotide sequence from a consensus sequence, or the "reference sequence." As used herein, the reference sequence of PLCG1 is the nucleotide sequence of SEQ ID NO:1 which corresponds to GI 11345540 (see Figure 1) and the reference sequence of PAI-2 is the nucleotide sequence of SEQ ID NO:3 which corresponds to GI 6705901 (see Figure 3).

To identify the location of each polymorphism in Table 3, a specific nucleotide residue in a reference sequence is listed for each polymorphism, where nucleotide residue number 1 is the first (*i.e.*, 5') nucleotide in GI 11345540 (the reference sequence for the PLCG1 gene, corresponding to SEQ ID NO:1), the first nucleotide in GI 6705901 (the reference sequence for the PAI-2 gene, corresponding to SEQ ID NO:3). Column 8

lists the reference sequence and polymorphic residue for each polymorphism.

Column 4 describes the type of variant for each SNP. Both of the SNPs of the instant invention result in a missense amino acid in the amino acid sequence of each protein. For example, as can be seen in Table 3, one polymorphism found in the population is a change from a cytidine to a thymidine in the PLCG1 gene at residue 64001 of GI 11345540 (polymorphism ID No. G329u1) (SEQ ID NO:5), or the complement thereof, which results in a change from an isoleucine to a threonine in the amino acid sequence of PLCG1 (SEQ ID NO:2) at amino acid residue 813. The second polymorphism is a change from a thymidine to a cytidine in the PAI-2 gene at residue 170871 of GI 6705901 (polymorphism ID No. PAI-2u1) (SEQ ID NO:6), or the complement thereof, which results in a change from an asparagine to aspartic acid in the amino acid sequence of PAI-2 (SEQ ID NO:4) at amino acid residue 120.

The nucleic acid molecules of the invention can be double- or single-stranded. Accordingly, the invention further provides for the complementary nucleic acid strands comprising the polymorphisms listed in Table 3.

The invention further provides allele-specific oligonucleotides that hybridize to a gene comprising a single nucleotide polymorphism or to the complement of the gene. Such oligonucleotides will hybridize to one polymorphic form of the nucleic acid molecules described herein but not to the other polymorphic form(s) of the sequence. Thus such oligonucleotides can be used to determine the presence or absence of particular alleles of the polymorphic sequences described herein. These oligonucleotides can be probes or primers.

Not only does the present invention provide polymorphisms in linkage disequilibrium with the polymorphisms of Table 3, it also provides methods for revealing the existence of yet other polymorphic regions in the human PLCG1 or PAI-2 gene. For example, the polymorphism studies described herein can also be applied to populations in which other vascular diseases or disorders are prevalent.

Other aspects of the invention are described below or will be apparent to one of skill in the art in light of the present disclosure.

Definitions

For convenience, the meaning of certain terms and phrases employed in the specification, examples, and appended claims are provided below.

The term "allele", which is used interchangeably herein with "allelic variant" refers to alternative forms of a gene or portions thereof. Alleles occupy the same locus or position on homologous chromosomes. When a subject has two identical alleles of a gene, the subject is said to be homozygous for the gene or allele. When a subject has two different alleles of a gene, the subject is said to be heterozygous for the gene or allele. Alleles of a specific gene, including the PLCG1 or PAI-2 genes, can differ from each other in a single nucleotide, or several nucleotides, and can include substitutions, deletions, and insertions of nucleotides. An allele of a gene can also be a form of a gene containing one or more mutations.

The term "allelic variant of a polymorphic region of a PLCG1 or a PAI-2 gene" refers to an alternative form of the PLCG1 or PAI-2 gene having one of several possible nucleotide sequences found in that region of the gene in the population.

"Biological activity" or "bioactivity" or "activity" or "biological function", which are used interchangeably, for the purposes herein when applied to PLCG1 or PAI-2, means an effector or antigenic function that is directly or indirectly performed by a PLCG1 or PAI-2 polypeptide (whether in its native or denatured conformation), or by a fragment thereof. Biological activities include modulation of the development of atherosclerotic plaque leading to vascular disease and other biological activities, whether presently known or inherent. A PLCG1 or PAI-2 bioactivity can be modulated by directly affecting a PLCG1 or PAI-2 protein effected by, for example, changing the level of effector or substrate level. Alternatively, a PLCG1 or PAI-2 bioactivity can be modulated by modulating the level of a PLCG1 or PAI-2 protein, such as by modulating expression of a PLCG1 or PAI-2 gene. Antigenic functions include possession of an

epitope or antigenic site that is capable of cross-reacting with antibodies that bind a native or denatured PLCG1 or PAI-2 polypeptide or fragment thereof.

Biologically active PLCG1 or PAI-2 polypeptides include polypeptides having both an effector and antigenic function, or only one of such functions. PLCG1 or PAI-2 polypeptides include antagonist polypeptides and native PLCG1 or PAI-2 polypeptides, provided that such antagonists include an epitope of a native PLCG1 or PAI-2 polypeptide. An effector function of PLCG1 or PAI-2 polypeptide can be the ability to bind to a ligand of a PLCG1 or PAI-2 molecule.

As used herein the term "bioactive fragment of a PLCG1 or PAI-2 protein" refers to a fragment of a full-length PLCG1 or PAI-2 protein, wherein the fragment specifically mimics or antagonizes the activity of a wild-type PLCG1 or PAI-2 protein. The bioactive fragment preferably is a fragment capable of binding to a second molecule, such as a ligand.

The term "an aberrant activity" or "abnormal activity", as applied to an activity of a protein such as PLCG1 or PAI-2, refers to an activity which differs from the activity of the wild-type (*i.e.*, normal or reference) protein or which differs from the activity of the protein in a healthy subject, *e.g.*, a subject not afflicted with a disease associated with a PLCG1 or PAI-2 allelic variant. An activity of a protein can be aberrant because it is stronger than the activity of its wild-type counterpart. Alternatively, an activity of a protein can be aberrant because it is weaker or absent relative to the activity of its wild-type counterpart. An aberrant activity can also be a change in reactivity. For example an aberrant protein can interact with a different protein or ligand relative to its wild-type counterpart. A cell can also have aberrant PLCG1 or PAI-2 activity due to overexpression or underexpression of the PLCG1 or PAI-2 gene. Aberrant PLCG1 or PAI-2 activity can result from a mutation in the gene, which results, *e.g.*, in lower or higher binding affinity of a ligand to the PLCG1 or PAI-2 protein encoded by the mutated gene. Aberrant PLCG1 or PAI-2 activity can also result from an abnormal PLCG1 or PAI-2 5' upstream regulatory element activity.

"Cells," "host cells" or "recombinant host cells" are terms used interchangeably herein. It is understood that such terms refer not only to the particular cell but to the progeny or derivatives of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

As used herein, the term "course of clinical therapy" refers to any chosen method to treat, prevent, or ameliorate a vascular disease, *e.g.,* CAD or MI, symptoms thereof, or related diseases or disorders. Courses of clinical therapy include, but are not limited to, lifestyle changes (*e.g.,* changes in diet or environment), administration of medication, use of surgical devices, such as, but not limited to, stents, angioplasty devices, used in, for example, percutaneous transluminal coronary balloon angioplasty (PTCA) or laser angioplasty, defibrillators, implantation of a stent, or other surgical intervention, such as, for example, coronary bypass grafting (CABG), or any combination thereof.

As used herein, the term "gene" or "recombinant gene" refers to a nucleic acid molecule comprising an open reading frame and including at least one exon and (optionally) an intron sequence. The term "intron" refers to a DNA sequence present in a given gene which is spliced out during mRNA maturation.

As used herein, the term "genetic profile" refers to the information obtained from identification of the specific alleles of a subject, *e.g.,* specific alleles within a polymorphic region of a particular gene or genes or proteins encoded by such genes. For example, a PLCG1 genetic profile refers to the specific alleles of a subject within the PLCG1 gene and a PAI-2 genetic profile refers to the specific alleles of a subject within the PAI-2 gene. For example, one can determine a subject's PLCG1 and/or PAI-2 genetic profile by determining the identity of the nucleotide present at nucleotide position 11345540 of SEQ ID NO:1 and/or the nucleotide present at nucleotide position 170871 of SEQ ID NO:3. One can also determine a subjects PLCG1 and/or PAI-2 genetic profile by determining the identity of the amino acid present at amino acid residue 813 of SEQ ID NO:2 and/or amino acid 120 of SEQ ID NO:4. The genetic

profile of a particular disease can be ascertained through identification of the identity of allelic variants in one or more genes which are associated with the particular disease.

"Homology" or "identity" or "similarity" refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. An "unrelated" or "non-homologous" sequence shares less than 40 % identity, though preferably less than 25 % identity, with one of the sequences of the present invention.

To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = number of identical positions/total number of positions (*e.g.*, overlapping positions) x100). In one embodiment the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with the

NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444-2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a *k*-tuple value of 2.

The term "a homolog of a nucleic acid" refers to a nucleic acid having a nucleotide sequence having a certain degree of homology with the nucleotide sequence of the nucleic acid or complement thereof. For example, a homolog of a double stranded nucleic acid having SEQ ID NO:N is intended to include nucleic acids having a nucleotide sequence which has a certain degree of homology with SEQ ID NO:N or with the complement thereof. Preferred homologs of nucleic acids are capable of hybridizing to the nucleic acid or complement thereof.

The term "hybridization probe" or "primer" as used herein is intended to include oligonucleotides which hybridize bind in a base-specific manner to a complementary strand of a target nucleic acid. Such probes include peptide nucleic acids, and described

in Nielsen *et al.*, (1991) *Science* 254:1497-1500. Probes and primers can be any length suitable for specific hybridization to the target nucleic acid sequence. The most appropriate length of the probe and primer may vary depending on the hybridization method in which it is being used; for example, particular lengths may be more appropriate for use in microfabricated arrays, while other lengths may be more suitable for use in classical hybridization methods. Such optimizations are known to the skilled artisan. Suitable probes and primers can range form about 5 nucleotides to about 30 nucleotides in length. For example, probes and primers can be 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 25, 26, 28 or 30 nucleotides in length. The probe or primer of the invention comprises a sequence that flanks and/or preferably overlaps, at least one polymorphic site occupied by any of the possible variant nucleotides. The nucleotide sequence of an overlapping probe or primer can correspond to the coding sequence of the allele or to the complement of the coding sequence of the allele.

The term "vascular disease or disorder" as used herein refers to any disease or disorder effecting the vascular system, including the heart and blood vessels. A vascular disease or disorder includes any disease or disorder characterized by vascular dysfunction, including, for example, intravascular stenosis (narrowing) or occlusion (blockage), due to the development of atherosclerotic plaque and diseases and disorders resulting therefrom. Examples of vascular diseases and disorders include, without limitation, atherosclerosis, CAD, MI, ischemia, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism.

The term "interact" as used herein is meant to include detectable interactions between molecules, such as can be detected using, for example, a binding or hybridization assay. The term interact is also meant to include "binding" interactions between molecules. Interactions may be, for example, protein-protein, protein-nucleic acid, protein-small molecule or small molecule-nucleic acid in nature.

The term "intronic sequence" or "intronic nucleotide sequence" refers to the nucleotide sequence of an intron or portion thereof.

The term "isolated" as used herein with respect to nucleic acids, such as DNA or RNA, refers to molecules separated from other DNAs or RNAs, respectively, that are present in the natural source of the macromolecule. The term isolated as used herein also refers to a nucleic acid or peptide that is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Moreover, an "isolated nucleic acid" is meant to include nucleic acid fragments which are not naturally occurring as fragments and would not be found in the natural state. The term "isolated" is also used herein to refer to polypeptides which are isolated from other cellular proteins and is meant to encompass both purified and recombinant polypeptides.

The term "linkage" describes the tendency of genes, alleles, loci or genetic markers to be inherited together as a result of their location on the same chromosome. It can be measured by percent recombination between the two genes, alleles, loci, or genetic markers. The term "linkage disequilibrium" refers to a greater than random association between specific alleles at two marker loci within a particular population. In general, linkage disequilibrium decreases with an increase in physical distance. If linkage disequilibrium exists between two markers, then the genotypic information at one marker can be used to make probabilistic predictions about the genotype of the second marker.

The term "locus" refers to a specific position in a chromosome. For example, a locus of a PLCG1 or PAI-2 gene refers to the chromosomal position of the PLCG1 or PAI-2 gene.

The term "modulation" as used herein refers to both upregulation, (*i.e.*, activation or stimulation), for example by agonizing; and downregulation (i.e. inhibition or suppression), for example by antagonizing of a bioactivity (*e.g.* expression of a gene).

The term "molecular structure" of a gene or a portion thereof refers to the structure as defined by the nucleotide content (including deletions, substitutions, additions of one or more nucleotides), the nucleotide sequence, the state of methylation, and/or any other modification of the gene or portion thereof.

The term "mutated gene" refers to an allelic form of a gene that differs from the predominant form in a population. A mutated gene is capable of altering the phenotype of a subject having the mutated gene relative to a subject having the predominant form of the gene. If a subject must be homozygous for this mutation to have an altered phenotype, the mutation is said to be recessive. If one copy of the mutated gene is sufficient to alter the phenotype of the subject, the mutation is said to be dominant. If a subject has one copy of the mutated gene and has a phenotype that is intermediate between that of a homozygous and that of a heterozygous subject (for that gene), the mutation is said to be co-dominant.

As used herein, the term "nucleic acid" refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include, as equivalents, derivatives, variants and analogs of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single (sense or antisense) and double-stranded polynucleotides. Deoxyribonucleotides include deoxyadenosine, deoxycytidine, deoxyguanosine, and deoxythymidine. For purposes of clarity, when referring herein to a nucleotide of a nucleic acid, which can be DNA or an RNA, the terms "adenine", "cytidine", "guanine", and thymidine" and/or "A", "C", "G", and "T", respectively, are used. It is understood that if the nucleic acid is RNA, a nucleotide having a uracil base is uridine.

The term "nucleotide sequence complementary to the nucleotide sequence set forth in SEQ ID NO:N" refers to the nucleotide sequence of the complementary strand of a nucleic acid strand having SEQ ID NO:N. The term "complementary strand" is used herein interchangeably with the term "complement". The complement of a nucleic acid strand can be the complement of a coding strand or the complement of a non-coding

strand. When referring to double stranded nucleic acids, the complement of a nucleic acid having SEQ ID NO:N refers to the complementary strand of the strand having SEQ ID NO:N or to any nucleic acid having the nucleotide sequence of the complementary strand of SEQ ID NO:N. When referring to a single stranded nucleic acid having the nucleotide sequence SEQ ID NO:N, the complement of this nucleic acid is a nucleic acid having a nucleotide sequence which is complementary to that of SEQ ID NO:N. The nucleotide sequences and complementary sequences thereof are always given in the 5' to 3' direction. The term "complement" and "reverse complement" are used interchangeably herein.

A "non-human animal" of the invention can include mammals such as rodents, non-human primates, sheep, goats, horses, dogs, cows, chickens, amphibians, reptiles, etc. Preferred non-human animals are selected from the rodent family including rat and mouse, most preferably mouse, though transgenic amphibians, such as members of the *Xenopus* genus, and transgenic chickens can also provide important tools for understanding and identifying agents which can affect, for example, embryogenesis and tissue formation. The term "chimeric animal" is used herein to refer to animals in which an exogenous sequence is found, or in which an exogenous sequence is expressed in some but not all cells of the animal. The term "tissue-specific chimeric animal" indicates that an exogenous sequence is present and/or expressed or disrupted in some tissues, but not others.

The term "oligonucleotide" is intended to include and single- or double stranded DNA or RNA. Oligonucleotides can be naturally occurring or synthetic, but are typically prepared by synthetic means. Preferred oligonucleotides of the invention include segments of PLCG1 or PAI-2 gene sequence or their complements, which include and/or flank any one of the polymorphic sites shown in Table 3. The segments can be between 5 and 250 bases, and, in specific embodiments, are between 5-10, 5-20, 10-20, 10-50, 20-50 or 10-100 bases. For example, the segments can be 21 bases. The polymorphic site can occur within any position of the segment or a region next to the

segment. The segments can be from any of the allelic forms of PLCG1 or PAI-2 gene sequence shown in Table 3.

The term "operably-linked" is intended to mean that the 5' upstream regulatory element is associated with a nucleic acid in such a manner as to facilitate transcription of the nucleic acid from the 5' upstream regulatory element.

The term "polymorphism" refers to the coexistence of more than one form of a gene or portion thereof. A portion of a gene of which there are at least two different forms, *i.e.,* two different nucleotide sequences, is referred to as a "polymorphic region of a gene." A polymorphic locus can be a single nucleotide, the identity of which differs in the other alleles. A polymorphic locus can also be more than one nucleotide long. The allelic form occurring most frequently in a selected population is often referred to as the reference and/or wildtype form. Other allelic forms are typically designated or alternative or variant alleles. Diploid organisms may be homozygous or heterozygous for allelic forms. A diallelic or biallelic polymorphism has two forms. A trialleleic polymorphism has three forms.

A "polymorphic gene" refers to a gene having at least one polymorphic region.

The term "primer" as used herein, refers to a single-stranded oligonucleotide which acts as a point of initiation of template-directed DNA synthesis under appropriate conditions (*e.g.,* in the presence of four different nucleoside triphosphates and as agent for polymerization, such as DNA or RNA polymerase or reverse transcriptase) in an appropriate buffer and at a suitable temperature. The length of a primer may vary but typically ranges from 15 to 30 nucleotides. A primer need not match the exact sequence of a template, but must be sufficiently complementary to hybridize with the template.

The term "primer pair" refers to a set of primers including an upstream primer that hybridizes with the 3' end of the complement of the DNA sequence to be amplified and a downstream primer that hybridizes with the 3' end of the sequence to be amplified.

The terms "protein", "polypeptide" and "peptide" are used interchangeably herein when referring to a gene product.

The term "recombinant protein" refers to a polypeptide which is produced by recombinant DNA techniques, wherein generally, DNA encoding the polypeptide is inserted into a suitable expression vector which is in turn used to transform a host cell to produce the heterologous protein.

A "regulatory element", also termed herein "regulatory sequence" is intended to include elements which are capable of modulating transcription from a 5' upstream regulatory sequence, including, but not limited to a basic promoter, and include elements such as enhancers and silencers. The term "enhancer", also referred to herein as "enhancer element", is intended to include regulatory elements capable of increasing, stimulating, or enhancing transcription from a 5' upstream regulatory element, including a basic promoter. The term "silencer", also referred to herein as "silencer element" is intended to include regulatory elements capable of decreasing, inhibiting, or repressing transcription from a 5' upstream regulatory element, including a basic promoter. Regulatory elements are typically present in 5' flanking regions of genes. Regulatory elements also may be present in other regions of a gene, such as introns. Thus, it is possible that PLCG1 or PAI-2 genes have regulatory elements located in introns, exons, coding regions, and 3' flanking sequences. Such regulatory elements are also intended to be encompassed by the present invention and can be identified by any of the assays that can be used to identify regulatory elements in 5' flanking regions of genes.

The term "regulatory element" further encompasses "tissue specific" regulatory elements, *i.e.*, regulatory elements which effect expression of an operably linked DNA sequence preferentially in specific cells (*e.g.*, cells of a specific tissue). Gene expression occurs preferentially in a specific cell if expression in this cell type is significantly higher than expression in other cell types. The term "regulatory element" also encompasses non-tissue specific regulatory elements, *i.e.*, regulatory elements which are active in most cell types. Furthermore, a regulatory element can be a constitutive regulatory element, *i.e.*, a regulatory element which constitutively regulates transcription, as opposed to a regulatory element which is inducible, *i.e.*, a regulatory element which is active primarily

in response to a stimulus. A stimulus can be, *e.g.*, a molecule, such as a protein, hormone, cytokine, heavy metal, phorbol ester, cyclic AMP (cAMP), or retinoic acid.

Regulatory elements are typically bound by proteins, *e.g.*, transcription factors. The term "transcription factor" is intended to include proteins or modified forms thereof, which interact preferentially with specific nucleic acid sequences, *i.e.*, regulatory elements, and which in appropriate conditions stimulate or repress transcription. Some transcription factors are active when they are in the form of a monomer. Alternatively, other transcription factors are active in the form of a dimer consisting of two identical proteins or different proteins (heterodimer). Modified forms of transcription factors are intended to refer to transcription factors having a postranslational modification, such as the attachment of a phosphate group. The activity of a transcription factor is frequently modulated by a postranslational modification. For example, certain transcription factors are active only if they are phosphorylated on specific residues. Alternatively, transcription factors can be active in the absence of phosphorylated residues and become inactivated by phosphorylation. A list of known transcription factors and their DNA binding site can be found, *e.g.*, in public databases, *e.g.*, TFMATRIX Transcription Factor Binding Site Profile database.

The term "single nucleotide polymorphism" (SNP) refers to a polymorphic site occupied by a single nucleotide, which is the site of variation between allelic sequences. The site is usually preceded by and followed by highly conserved sequences of the allele (*e.g.*, sequences that vary in less than 1/100 or 1/1000 members of a population). A SNP usually arises due to substitution of one nucleotide for another at the polymorphic site. SNPs can also arise from a deletion of a nucleotide or an insertion of a nucleotide relative to a reference allele. Typically the polymorphic site is occupied by a base other than the reference base. For example, where the reference allele contains the base "T" (thymidine) at the polymorphic site, the altered allele can contain a "C" (cytidine), "G" (guanine), or "A" (adenine) at the polymorphic site.

SNP's may occur in protein-coding nucleic acid sequences, in which case they may give rise to a defective or otherwise variant protein, or genetic disease. Such a SNP may alter the coding sequence of the gene and therefore specify another amino acid (a "missense" SNP) or a SNP may introduce a stop codon (a "nonsense" SNP). When a SNP does not alter the amino acid sequence of a protein, the SNP is called "silent." SNP's may also occur in noncoding regions of the nucleotide sequence. This may result in defective protein expression, *e.g.*, as a result of alternative spicing, or it may have no effect.

As used herein, the term "specifically hybridizes" or "specifically detects" refers to the ability of a nucleic acid molecule of the invention to hybridize to at least approximately 6, 8, 10, 12, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130 or 140 consecutive nucleotides of either strand of a PLCG1 or PAI-2 gene.

As used herein, the term "transfection" means the introduction of a nucleic acid, *e.g.*, an expression vector, into a recipient cell by nucleic acid-mediated gene transfer. The term "transduction" is generally used herein when the transfection with a nucleic acid is by viral delivery of the nucleic acid. "Transformation", as used herein, refers to a process in which a cell's genotype is changed as a result of the cellular uptake of exogenous DNA or RNA, and, for example, the transformed cell expresses a recombinant form of a polypeptide or, in the case of anti-sense expression from the transferred gene, the expression of a naturally-occurring form of the recombinant protein is disrupted.

As used herein, the term "transgene" refers to a nucleic acid sequence which has been genetic-engineered into a cell. Daughter cells deriving from a cell in which a transgene has been introduced are also said to contain the transgene (unless it has been deleted). A transgene can encode, *e.g.*, a polypeptide, or an antisense transcript, partly or entirely heterologous, *i.e.*, foreign, to the transgenic animal or cell into which it is introduced, or, is homologous to an endogenous gene of the transgenic animal or cell into which it is introduced, but which is designed to be inserted, or is inserted, into the animal's genome in such a way as to alter the genome of the cell into which it is inserted

(*e.g.*, it is inserted at a location which differs from that of the natural gene or its insertion results in a knockout). Alternatively, a transgene can also be present in an episome. A transgene can include one or more transcriptional regulatory sequence and any other nucleic acid, (*e.g.* intron), that may be necessary for optimal expression of a selected nucleic acid.

A "transgenic animal" refers to any animal, preferably a non-human animal, *e.g.* a mammal, bird or an amphibian, in which one or more of the cells of the animal contain heterologous nucleic acid introduced by genetic engineering, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or *in vitro* fertilization, but rather is directed to the introduction of a recombinant DNA molecule. This molecule may be integrated within a chromosome, or it may be extrachromosomally replicating DNA. In the typical transgenic animals described herein, the transgene causes cells to express a recombinant form of one of a protein, *e.g.* either agonistic or antagonistic forms. However, transgenic animals in which the recombinant gene is silent are also contemplated, as for example, the FLP or CRE recombinase dependent constructs described below. Moreover, "transgenic animal" also includes those recombinant animals in which gene disruption of one or more genes is caused by human intervention, including both recombination and antisense techniques.

The term "treatment", or "treating" as used herein, is defined as the application or administration of a therapeutic agent to a subject, implementation of lifestyle changes (*e.g.*, changes in diet or environment), administration of medication, use of surgical devices, such as, but not limited to, stents, defibrillators, and/or angioplasty devices, and/or surgical procedures, such as, for example, percutaneous transluminal coronary balloon angioplasty (PTCA) or laser angioplasty, implantation of a stent, or other surgical intervention or procedure, such as, for example, coronary bypass grafting (CABG), or any combination thereof, or application or administration of a therapeutic

agent to an isolated tissue or cell line from a subject, who has a disease or disorder, a symptom of disease or disorder or a predisposition toward a disease or disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disease or disorder, the symptoms of the disease or disorder, or the predisposition toward disease.

As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting or replicating another nucleic acid to which it has been linked. One type of preferred vector is an episome, *i.e.*, a nucleic acid capable of extra-chromosomal replication. Preferred vectors are those capable of autonomous replication and/or expression of nucleic acids to which they are linked. Vectors capable of directing the expression of genes to which they are operatively-linked are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of "plasmids" which refer generally to circular double stranded DNA circles which, in their vector form are not physically linked to the host chromosome. In the present specification, "plasmid" and "vector" are used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors which serve equivalent functions and which become known in the art subsequently hereto.

Polymorphisms Used in the Methods of the Invention

The nucleic acid molecules of the present invention include specific allelic variants of the PLCG1 gene and the PAI-2 gene, which differ from the reference sequences set forth in SEQ ID NO:1 or SEQ ID NO:3, respectively, or at least a portion thereof, having a polymorphic region. The preferred nucleic acid molecules of the present invention comprise PLCG1 and PAI-2 sequences having one or more of the polymorphisms shown in Table 3 (SEQ ID NOs:5 and 6), and those in linkage disequilibrium therewith. The invention further comprises isolated nucleic acid molecules complementary to nucleic acid molecules comprising the polymorphisms of the present invention. Nucleic acid molecules of the present invention can function as

probes or primers, *e.g.*, in methods for determining the allelic identity of a PLCG1 or PAI-2 polymorphic region. The nucleic acids of the invention can also be used, singly, or, preferably, in combination, to determine whether a subject is or is not at risk of developing a disease associated with a specific allelic variant of a PLCG1 or PAI-2 polymorphic region, *e.g*, a vascular disease or disorder. The nucleic acids of the invention can further be used to prepare or express PLCG1 or PAI-2 polypeptides encoded by specific alleles, such as mutant alleles. Such nucleic acids can be used in gene therapy. Polypeptides encoded by specific PLCG1 or PAI-2 alleles, such as mutant PLCG1 or PAI-2 polypeptides, can also be used in therapy or for preparing reagents, *e.g.*, antibodies, for detecting PLCG1 or PAI-2 proteins encoded by these alleles. Accordingly, such reagents can be used to detect mutant PLCG1 or PAI-2 proteins.

As described herein, allelic variants of human PLCG1 or PAI-2 genes have been identified. The invention is intended to encompass these allelic variants as well as, those in linkage disequilibrium which can be identified, *e.g.*, according to the methods described herein. "Linkage disequilibrium" refers to an association between specific alleles at two marker loci within a particular population. In general, linkage disequilbrium decreases with an increase in physical distance. If linkage disequilbrium exists between two markers, then the genotypic information at one marker can be used to make predictions about the genotype of the second marker.

The invention also provides isolated nucleic acids comprising at least one polymorphic region of a PLCG1 or PAI-2 gene having a nucleotide sequence which differs from the reference nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:3, respectively. Preferred nucleic acids have a variant allele located in the coding region of the PLCG1 or PAI-2 gene. Accordingly, preferred nucleic acids of the invention comprise a thymidine at residue 64001 of GI 11345540 (as set forth in SEQ ID NO:1), or the complement thereof, or a cytidine at residue 170871 of GI 6705901 (as set forth in SEQ ID NO:3), or the complement thereof. Preferred nucleic acids used in combination in the methods of the invention to predict the risk of vascular diseases or disorders comprise thymidine at residue 64001 of GI 11345540 (as set forth in SEQ ID

NO:1) and a thymidine at residue 170871 of GI 6705901 (as set forth in SEQ ID NO:3), or the complements thereof. Preferred nucleic acids can also have a polymorphic region in an upstream regulatory element, an exon, or in the 3' UTR.

The nucleic acid molecules of the present invention can be single stranded DNA (*e.g.*, an oligonucleotide), double stranded DNA (*e.g.*, double stranded oligonucleotide) or RNA. Preferred nucleic acid molecules of the invention can be used as probes or primers. Primers of the invention refer to nucleic acids which hybridize to a nucleic acid sequence which is adjacent to the region of interest or which covers the region of interest and is extended. As used herein, the term "hybridizes" is intended to describe conditions for hybridization and washing under which nucleotide sequences that are significantly identical or homologous to each other remain hybridized to each other. Preferably, the conditions are such that sequences at least about 70%, more preferably at least about 80%, even more preferably at least about 85% or 90% identical to each other remain hybridized to each other. Such stringent conditions vary according to the length of the involved nucleotide sequence but are known to those skilled in the art and can be found or determined based on teachings in *Current Protocols in Molecular Biology*, Ausubel *et al.*, eds., John Wiley & Sons, Inc. (1995), sections 2, 4 and 6. Additional stringent conditions and formulas for determining such conditions can be found in *Molecular Cloning: A Laboratory Manual*, Sambrook *et al.*, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989), chapters 7; 9 and 11. A preferred, non-limiting example of stringent hybridization conditions for hybrids that are at least basepairs in length includes hybridization in 4X sodium chloride/sodium citrate (SSC), at about 65-70°C (or hybridization in 4X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 1X SSC, at about 65-70°C. A preferred, non-limiting example of highly stringent hybridization conditions for such hybrids includes hybridization in 1X SSC, at about 65-70°C (or hybridization in 1X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 0.3X SSC, at about 65-70°C. A preferred, non-limiting example of reduced stringency hybridization conditions for such hybrids includes hybridization in 4X SSC, at about 50-60°C (or alternatively hybridization in 6X

SSC plus 50% formamide at about 40-45°C) followed by one or more washes in 2X SSC, at about 50-60°C. Ranges intermediate to the above-recited values, *e.g.*, at 65-70° C or at 42-50°C are also intended to be encompassed by the present invention. SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes each after hybridization is complete.

The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, $T_m(°C) = 2(\#\text{ of A + T bases}) + 4(\#\text{ of G + C bases})$. For hybrids between 18 and 49 base pairs in length, $T_m(°C) = 81.5 + 16.6(\log_{10}[Na^+]) + 0.41(\%G+C) - (600/N)$, where N is the number of bases in the hybrid, and $[Na^+]$ is the concentration of sodium ions in the hybridization buffer ($[Na^+]$ for 1xSSC = 0.165 M). It will also be recognized by the skilled practitioner that additional reagents may be added to hybridization and/or wash buffers to decrease non-specific hybridization of nucleic acid molecules to membranes, for example, nitrocellulose or nylon membranes, including but not limited to blocking agents (*e.g.*, BSA or salmon or herring sperm carrier DNA), detergents (*e.g.*, SDS), chelating agents (*e.g.*, EDTA), Ficoll, PVP and the like. When using nylon membranes, in particular, an additional preferred, non-limiting example of stringent hybridization conditions is hybridization in 0.25-0.5M NaH_2PO_4, 7% SDS at about 65°C, followed by one or more washes at 0.02M NaH_2PO_4, 1% SDS at 65°C, see *e.g.*, Church and Gilbert (1984) *Proc. Natl. Acad. Sci. USA* 81:1991-1995, (or alternatively 0.2X SSC, 1% SDS).

A primer or probe can be used alone in a detection method, or a primer can be used together with at least one other primer or probe in a detection method. Primers can also be used to amplify at least a portion of a nucleic acid. Probes of the invention refer to nucleic acids which hybridize to the region of interest and which are not further extended. For example, a probe is a nucleic acid which specifically hybridizes to a

polymorphic region of a PLCG1 or PAI-2 gene, and which by hybridization or absence of hybridization to the DNA of a subject or the type of hybrid formed will be indicative of the identity of the allelic variant of the polymorphic region of the PLCG1 or PAI-2 gene.

Numerous procedures for determining the nucleotide sequence of a nucleic acid molecule, or for determining the presence of mutations in nucleic acid molecules include a nucleic acid amplification step, which can be carried out by, *e.g.*, polymerase chain reaction (PCR). Accordingly, in one embodiment, the invention provides primers for amplifying portions of a PLCG1 or PAI-2 gene, such as portions of exons and/or portions of introns. In a preferred embodiment, the exons and/or sequences adjacent to the exons of the human PLCG1 or PAI-2 gene will be amplified to, *e.g.*, detect which allelic variant, if any, of a polymorphic region is present in the PLCG1 or PAI-2 gene of a subject. Preferred primers comprise a nucleotide sequence complementary a specific allelic variant of a PLCG1 or PAI-2 polymorphic region and of sufficient length to selectively hybridize with a PLCG1 or PAI-2 gene. In a preferred embodiment, the primer, *e.g.*, a substantially purified oligonucleotide, comprises a region having a nucleotide sequence which hybridizes under stringent conditions to about 6, 8, 10, or 12, preferably 25, 30, 40, 50, or 75 consecutive nucleotides of a PLCG1 or PAI-2 gene. In an even more preferred embodiment, the primer is capable of hybridizing to a PLCG1 or PAI-2 nucleotide sequence, complements thereof, allelic variants thereof, or complements of allelic variants thereof. For example, primers comprising a nucleotide sequence of at least about 15 consecutive nucleotides, at least about 25 nucleotides or having from about 15 to about 20 nucleotides set forth in any of SEQ ID NOs:5 and SEQ ID NO:6 or complement thereof are provided by the invention. Primers having a sequence of more than about 25 nucleotides are also within the scope of the invention. Preferred primers of the invention are primers that can be used in PCR for amplifying each of the exons of a PLCG1 or PAI-2 gene.

Primers can be complementary to nucleotide sequences located close to each other or further apart, depending on the use of the amplified DNA. For example, primers can be chosen such that they amplify DNA fragments of at least about 10 nucleotides or as much as several kilobases. Preferably, the primers of the invention will hybridize selectively to PLCG1 or PAI-2 nucleotide sequences located about 150 to about 350 nucleotides apart.

For amplifying at least a portion of a nucleic acid, a forward primer (*i.e.*, 5' primer) and a reverse primer (*i.e.*, 3' primer) will preferably be used. Forward and reverse primers hybridize to complementary strands of a double stranded nucleic acid, such that upon extension from each primer, a double stranded nucleic acid is amplified. A forward primer can be a primer having a nucleotide sequence or a portion of the nucleotide sequence shown in Table 3 (*e.g.*, SEQ ID NO:5 and SEQ ID NO:6). A reverse primer can be a primer having a nucleotide sequence or a portion of the nucleotide sequence that is complementary to a nucleotide sequence shown in Table 3 (*e.g.*, SEQ ID NO:5 and SEQ ID NO:6).

Yet other preferred primers of the invention are nucleic acids which are capable of selectively hybridizing to an allelic variant of a polymorphic region of a PLCG1 or PAI-2 gene. Thus, such primers can be specific for a PLCG1 or PAI-2 gene sequence, so long as they have a nucleotide sequence which is capable of hybridizing to a PLCG1 or PAI-2 gene. Preferred primers are capable of specifically hybridizing to any of the allelic variants listed in Table 3. Such primers can be used, *e.g.*, in sequence specific oligonucleotide priming as described further herein.

Other preferred primers used in the methods of the invention are nucleic acids which are capable of hybridizing to the reference sequence of a PLCG1 or PAI-2 gene, thereby detecting the presence of the reference allele of an allelic variant or the absence of a variant allele of an allelic variant in the PLCG1 or PAI-2 genes. Such primers can be used in combination, *e.g.*, primers specific for the variant polynucleotide of the PLGC1 gene and primers specific for the reference polynucleotide of the PAI-2 gene can be used in combination. The sequences of primers specific for the reference sequences

comprising the PLCG1 gene or the PAI-2 gene will be readily apparent to one of skill in the art.

The PLCG1 or PAI-2 nucleic acids of the invention can also be used as probes, *e.g.*, in therapeutic and diagnostic assays. For instance, the present invention provides a probe comprising a substantially purified oligonucleotide, which oligonucleotide comprises a region having a nucleotide sequence that is capable of hybridizing specifically to a region of a PLCG1 or PAI-2 gene which is polymorphic (*e.g.*, SEQ ID NO:5 and SEQ ID NO:6). In an even more preferred embodiment of the invention, the probes are capable of hybridizing specifically to one allelic variant of a PLCG1 or PAI-2 gene having a nucleotide sequence which differs from the nucleotide sequence set forth in SEQ ID NO:1 or 3. Such probes can then be used to specifically detect which allelic variant of a polymorphic region of a PLCG1 or PAI-2 gene is present in a subject. The polymorphic region can be located in the 5' upstream regulatory element, exon, or intron sequences of a PLCG1 or PAI-2 gene.

Particularly, preferred probes of the invention have a number of nucleotides sufficient to allow specific hybridization to the target nucleotide sequence. Where the target nucleotide sequence is present in a large fragment of DNA, such as a genomic DNA fragment of several tens or hundreds of kilobases, the size of the probe may have to be longer to provide sufficiently specific hybridization, as compared to a probe which is used to detect a target sequence which is present in a shorter fragment of DNA. For example, in some diagnostic methods, a portion of a PLCG1 or PAI-2 gene may first be amplified and thus isolated from the rest of the chromosomal DNA and then hybridized to a probe. In such a situation, a shorter probe will likely provide sufficient specificity of hybridization. For example, a probe having a nucleotide sequence of about 10 nucleotides may be sufficient.

In preferred embodiments, the probe or primer further comprises a label attached thereto, which, *e.g.*, is capable of being detected, *e.g.* the label group is selected from amongst radioisotopes, fluorescent compounds, enzymes, and enzyme co-factors.

In a preferred embodiment of the invention, the isolated nucleic acid, which is used, *e.g.*, as a probe or a primer, is modified, so as to be more stable than naturally occurring nucleotides. Exemplary nucleic acid molecules which are modified include phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Patent Numbers 5,176,996; 5,264,564; and 5,256,775).

The nucleic acids of the invention can also be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule. The nucleic acids, *e.g.*, probes or primers, may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, (1989) *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556; Lemaitre *et al.*, (1987) *Proc. Natl. Acad. Sci. U.S.A.* 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988), hybridization-triggered cleavage agents. (See, *e.g.*, Krol *et al.*, (1988) *BioTechniques* 6:958-976) or intercalating agents (See, *e.g.*, Zon, (1988) *Pharm. Res.* 5:539-549). To this end, the nucleic acid of the invention may be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The isolated nucleic acid comprising a PLCG1 or PAI-2 intronic sequence may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytidine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytidine, 5-methylcytidine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytidine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-

oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The isolated nucleic acid may also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the nucleic acid comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet a further embodiment, the nucleic acid is an α-anomeric oligonucleotide. An α-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gautier *et al.*, 1987, *Nucl. Acids Res.* 15:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue *et al.*, (1987) *Nucl. Acids Res.* 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue *et al.*, (1987) *FEBS Lett.* 215:327-330).

Any nucleic acid fragment of the invention can be prepared according to methods well known in the art and described, *e.g.,* in Sambrook, J. Fritsch, E.F., and Maniatis, T. (1989) *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. For example, discrete fragments of the DNA can be prepared and cloned using restriction enzymes. Alternatively, discrete fragments can be prepared using the Polymerase Chain Reaction (PCR) using primers having an appropriate sequence.

Oligonucleotides of the invention may be synthesized by standard methods known in the art, *e.g.* by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein *et al.* ((1988) *Nucl. Acids Res.* 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin *et al.*, (1988), *Proc. Natl. Acad. Sci. U.S.A.* 85:7448-7451), etc.

The invention also provides vectors and plasmids comprising the nucleic acids of the invention. For example, in one embodiment, the invention provides a vector comprising at least a portion of the PLCG1 gene or the PAI-2 gene comprising a polymorphic region. Thus, the invention provides vectors for expressing at least a portion of the newly identified allelic variants of the human PLCG1 gene or PAI-2 gene reference, as well as other allelic variants, comprising a nucleotide sequence which is different from the nucleotide sequence disclosed in GI 11345540 or GI 6705901, respectively. The allelic variants can be expressed in eukaryotic cells, *e.g.*, cells of a subject, or in prokaryotic cells.

In one embodiment, the vector comprising at least a portion of a PLCG1 or PAI-2 allele is introduced into a host cell, such that a protein encoded by the allele is synthesized. The PLCG1 or PAI-2 protein produced can be used, *e.g.*, for the production of antibodies, which can be used, *e.g.*, in methods for detecting mutant forms of PLCG1 or PAI-2. Alternatively, the vector can be used for gene therapy, and be, *e.g.*, introduced into a subject to produce PLCG1 or PAI-2 protein. Host cells comprising a vector having at least a portion of a PLCG1 or PAI-2 gene are also within the scope of the invention.

Polypeptides of the invention

The present invention provides isolated PLCG1 or PAI-2 polypeptides, such as PLCG1 or PAI-2 polypeptides which are encoded by specific allelic variants of PLCG1 or PAI-2, including those identified herein. The amino acid sequences of the PLCG1 or PAI-2 proteins have been deduced. The PLCG1 gene encodes a 1,290 amino acid protein and is described in, for example, Stahl, M. L., *et al.* (1988) *Nature* 332: 269-272. The PAI-2 gene encodes a 450 amino acid protein and is described in, for example, Antalis, T. M, *et al.* (1988) *Proc. Nat. Acad. Sci.* 85: 985-989. The polymorphisms of the present invention are missense mutations which result in the change of an amino acid in the amino acid sequence of the PLCG1 gene and in the PAI-2 gene.

As shown in Table 3, one polymorphism found in the population screened is a change from a cytidine (C) to a thymidine (T) in the PLCG1 gene at residue 64001 of the reference sequence GI 11345540 (polymorphism ID No. G329u1), or the complement thereof, which results in a change from a isoleucine to a threonine in the amino acid sequence of PLCG1 (SEQ ID NO:2) at amino acid residue 813. A second polymorphism is a change from a thymidine (T) to a cytidine (C) in at residue 170871 of the reference sequence GI 6705901 (polymorphism ID No. PAI2u1), or the complement thereof, which results in a change from an asparagine to an aspartic acid in the amino acid sequence of PAI-2 (SEQ ID NO:4) at amino acid residue 120.

In one embodiment, the PLCG1 or PAI-2 polypeptides are isolated from, or otherwise substantially free of other cellular proteins. The term "substantially free of other cellular proteins" (also referred to herein as "contaminating proteins") or "substantially pure or purified preparations" are defined as encompassing preparations of PLCG1 or PAI-2 polypeptides having less than about 20% (by dry weight) contaminating protein, and preferably having less than about 5% contaminating protein. It will be appreciated that functional forms of the subject polypeptides can be prepared, for the first time, as purified preparations by using a cloned gene as described herein.

Preferred PLCG1 or PAI-2 proteins of the invention have an amino acid sequence which is at least about 60%, 70%, 80%, 85%, 90%, or 95% identical or homologous to the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4, respectively. Even more preferred PLCG1 or PAI-2 proteins comprise an amino acid sequence which is at least about 95%, 96%, 97%, 98%, or 99% homologous or identical to the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4, respectively. Such proteins can be recombinant proteins, and can be, *e.g.,* produced *in vitro* from nucleic acids comprising a specific allele of a PLCG1 or PAI-2 polymorphic region. For example, recombinant polypeptides preferred by the present invention can be encoded by a nucleic acid which comprises a sequence which is at least 85% homologous and more preferably 90% homologous and most preferably 95% homologous with a nucleotide sequence set forth in SEQ ID NOs:1 or 3 and comprises an allele of a polymorphic region that differs from

that set forth in SEQ ID NOs:1 or 3. Polypeptides which are encoded by a nucleic acid comprising a sequence that is at least about 98-99% homologous with the sequence of SEQ ID NOs:1 or 3 and comprises an allele of a polymorphic region that differs from that set forth in SEQ ID NOs:1 or 3 are also within the scope of the invention.

In a preferred embodiment, a PLCG1 or PAI-2 protein of the present invention is a mammalian PLCG1 or PAI-2 protein. In an even more preferred embodiment, the PLCG1 or PAI-2 protein is a human protein.

The invention also provides peptides that preferably are capable of functioning in one of either role of an agonist or antagonist of at least one biological activity of a reference ("normal") PLCG1 or PAI-2 protein of the appended sequence listing. The term "evolutionarily related to," with respect to amino acid sequences of PLCG1 or PAI-2 proteins, refers to both polypeptides having amino acid sequences found in human populations, and also to artificially produced mutational variants of human PLCG1 or PAI-2 polypeptides which are derived, for example, by combinatorial mutagenesis.

Full length proteins or fragments corresponding to one or more particular motifs and/or domains or to arbitrary sizes, for example, at least 5, 10, 25, 50, 75 and 100, amino acids in length of PLCG1 or PAI-2 protein are within the scope of the present invention.

Isolated PLCG1 or PAI-2 peptides or polypeptides can be obtained by screening peptides recombinantly produced from the corresponding fragment of the nucleic acid encoding such peptides. In addition, such peptides and polypeptides can be chemically synthesized using techniques known in the art such as conventional Merrifield solid phase f-Moc or t-Boc chemistry. For example, a PLCG1 or PAI-2 peptide or polypeptide of the present invention may be arbitrarily divided into fragments of desired length with no overlap of the fragments, or preferably divided into overlapping fragments of a desired length. The fragments can be produced (recombinantly or by chemical synthesis) and tested to identify those peptides or polypeptides which can function as either agonists or antagonists of a wild-type (*e.g.*, "normal") PLCG1 or PAI-2 protein.

In general, peptides and polypeptides referred to herein as having an activity (*e.g.*, are "bioactive") of a PLCG1 or PAI-2 protein are defined as peptides and polypeptides which mimic or antagonize all or a portion of the biological/biochemical activities of a PLCG1 or PAI-2 protein having SEQ ID NO:2 or SEQ ID NO:4, respectively, such as the ability to bind ligands. Other biological activities of the subject PLCG1 or PAI-2 proteins are described herein or will be reasonably apparent to those skilled in the art. According to the present invention, a peptide or polypeptide has biological activity if it is a specific agonist or antagonist of a naturally-occurring form of a PLCG1 or PAI-2 protein.

Assays for determining whether a PLCG1 or PAI-2 protein or variant thereof, has one or more biological activities are well known in the art.

Other preferred proteins of the invention are those encoded by the nucleic acids set forth in the section pertaining to nucleic acids of the invention. In particular, the invention provides fusion proteins, *e.g.*, PLCG1 or PAI-2-immunoglobulin fusion proteins. Such fusion proteins can provide, *e.g.*, enhanced stability and solubility of PLCG1 or PAI-2 proteins and may thus be useful in therapy. Fusion proteins can also be used to produce an immunogenic fragment of a PLCG1 or PAI-2 protein. For example, the VP6 capsid protein of rotavirus can be used as an immunologic carrier protein for portions of the PLCG1 or PAI-2 polypeptide, either in the monomeric form or in the form of a viral particle. The nucleic acid sequences corresponding to the portion of a subject PLCG1 or PAI-2 protein to which antibodies are to be raised can be incorporated into a fusion gene construct which includes coding sequences for a late vaccinia virus structural protein to produce a set of recombinant viruses expressing fusion proteins comprising PLCG1 or PAI-2 epitopes as part of the virion. It has been demonstrated with the use of immunogenic fusion proteins utilizing the Hepatitis B surface antigen fusion proteins that recombinant Hepatitis B virions can be utilized in this role as well. Similarly, chimeric constructs coding for fusion proteins containing a portion of a PLCG1 or PAI-2 protein and the poliovirus capsid protein can be created to enhance immunogenicity of the set of polypeptide antigens (see, for example, EP Publication No:

0259149; and Evans *et al.* (1989) *Nature* 339:385; Huang *et al.* (1988) *J. Virol.* 62:3855; and Schlienger *et al.* (1992) *J. Virol.* 66:2).

The Multiple antigen peptide system for peptide-based immunization can also be utilized to generate an immunogen, wherein a desired portion of a PLCG1 or PAI-2 polypeptide is obtained directly from organo-chemical synthesis of the peptide onto an oligomeric branching lysine core (see, for example, Posnett *et al.* (1988) JBC 263:1719 and Nardelli *et al.* (1992) *J. Immunol.* 148:914). Antigenic determinants of PLCG1 or PAI-2 proteins can also be expressed and presented by bacterial cells.

Fusion proteins can also facilitate the expression of proteins including the PLCG1 or PAI-2 polypeptides of the present invention. For example, PLCG1 or PAI-2 polypeptides can be generated as glutathione-S-transferase (GST-fusion) proteins. Such GST-fusion proteins can be easily purified, as for example by the use of glutathione-derivatized matrices (see, for example, Current Protocols in Molecular Biology, eds. Ausubel *et al.* (N.Y.: John Wiley & Sons, 1991)) and used subsequently to yield purified PLCG1 or PAI-2 polypeptides.

The present invention further pertains to methods of producing the subject PLCG1 or PAI-2 polypeptides. For example, a host cell transfected with a nucleic acid vector directing expression of a nucleotide sequence encoding the subject polypeptides can be cultured under appropriate conditions to allow expression of the peptide to occur. Suitable media for cell culture are well known in the art. The recombinant PLCG1 or PAI-2 polypeptide can be isolated from cell culture medium, host cells, or both using techniques known in the art for purifying proteins including ion-exchange chromatography, gel filtration chromatography, ultrafiltration, electrophoresis, and immunoaffinity purification with antibodies specific for such peptide. In a preferred embodiment, the recombinant PLCG1 or PAI-2 polypeptide is a fusion protein containing a domain which facilitates its purification, such as GST fusion protein.

Moreover, it will be generally appreciated that, under certain circumstances, it may be advantageous to provide homologs of one of the subject PLCG1 or PAI-2 polypeptides which function in a limited capacity as one of either a PLCG1 or PAI-2

agonist (mimetic) or a PLCG1 or PAI-2 antagonist, in order to promote or inhibit only a subset of the biological activities of the naturally-occurring form of the protein. Thus, specific biological effects can be elicited by treatment with a homolog of limited function, and with fewer side effects relative to treatment with agonists or antagonists which are directed to all of the biological activities of naturally occurring forms of PLCG1 or PAI-2 proteins.

Homologs of each of the subject PLCG1 or PAI-2 proteins can be generated by mutagenesis, such as by discrete point mutation(s), and/or by truncation. For instance, mutation can give rise to homologs which retain substantially the same, or merely a subset, of the biological activity of the PLCG1 or PAI-2 polypeptide from which it was derived. Alternatively, antagonistic forms of the protein can be generated which are able to inhibit the function of the naturally occurring form of the protein, such as by competitively binding to a PLCG1 or PAI-2 receptor.

The recombinant PLCG1 or PAI-2 polypeptides of the present invention also include homologs of PLCG1 or PAI-2 polypeptides which differ from the PLCG1 or PAI-2 protein having SEQ ID NO:2 or SEQ ID NO:4, respectively, such as versions of the protein which are resistant to proteolytic cleavage, as for example, due to mutations which alter ubiquitination or other enzymatic targeting associated with the protein.

PLCG1 or PAI-2 polypeptides may also be chemically modified to create PLCG1 or PAI-2 derivatives by forming covalent or aggregate conjugates with other chemical moieties, such as glycosyl groups, lipids, phosphate, acetyl groups and the like. Covalent derivatives of PLCG1 or PAI-2 proteins can be prepared by linking the chemical moieties to functional groups on amino acid side-chains of the protein or at the N-terminus or at the C-terminus of the polypeptide.

Modification of the structure of the subject PLCG1 or PAI-2 polypeptides can be for such purposes as enhancing therapeutic or prophylactic efficacy, stability (*e.g.*, ex vivo shelf life and resistance to proteolytic degradation), or post-translational modifications (*e.g.*, to alter phosphorylation pattern of protein). Such modified peptides, when designed to retain at least one activity of the naturally-occurring form of the

protein, or to produce specific antagonists thereof, are considered functional equivalents of the PLCG1 or PAI-2 polypeptides described in more detail herein. Such modified peptides can be produced, for instance, by amino acid substitution, deletion, or addition. The substitutional variant may be a substituted conserved amino acid or a substituted non-conserved amino acid.

For example, it is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid (*i.e.*, isosteric and/or isoelectric mutations) will not have a major effect on the biological activity of the resulting molecule. Conservative replacements are those that take place within a family of amino acids that are related in their side chains. Genetically encoded amino acids can be divided into four families: (1) acidic = aspartate, glutamate; (2) basic = lysine, arginine, histidine; (3) nonpolar = alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and (4) uncharged polar = glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. In similar fashion, the amino acid repertoire can be grouped as (1) acidic = aspartate, glutamate; (2) basic = lysine, arginine histidine, (3) aliphatic = glycine, alanine, valine, leucine, isoleucine, serine, threonine, with serine and threonine optionally be grouped separately as aliphatic-hydroxyl; (4) aromatic = phenylalanine, tyrosine, tryptophan; (5) amide = asparagine, glutamine; and (6) sulfur -containing = cysteine and methionine. (see, for example, Biochemistry, 2nd ed., Ed. by L. Stryer, WH Freeman and Co.: 1981). Whether a change in the amino acid sequence of a peptide results in a functional PLCG1 or PAI-2 homolog (*e.g.*, functional in the sense that the resulting polypeptide mimics or antagonizes the wild-type form) can be readily determined by assessing the ability of the variant peptide to produce a response in cells in a fashion similar to the wild-type protein, or competitively inhibit such a response. Polypeptides in which more than one replacement has taken place can readily be tested in the same manner.

Methods

The invention further provides predictive medicine methods, which are based, at least in part, on the discovery of PLCG1 or PAI-2 polymorphic regions which are associated with specific physiological states and/or diseases or disorders, *e.g.*, vascular diseases or disorders such as CAD and MI. These methods can be used alone, or in combination with other predictive medicine methods, including the identification and analysis of known risk factors associated with vascular disease, *e.g.*, phenotypic factors such as, for example, obesity, diabetes and family history.

For example, information obtained using the diagnostic assays described herein (singly or in combination with information of another genetic defect which contributes to the same disease, *e.g.*, a vascular disease or disorder) is useful for diagnosing or confirming that a subject has an allele of a polymorphic region which is associated with a particular disease or disorder, *e.g.*, a vascular disease or disorder. Moreover, the information obtained using the diagnostic assays described herein, singly or in combination with information of another genetic defect which contributes to the same disease, *e.g.*, a vascular disease or disorder, can be used to predict whether or not a subject will benefit from further diagnostic evaluation for a vascular disease or disorder. Such further diagnostic evaluation includes, but is not limited to, cardiovascular imaging, such as angiography, cardiac ultrasound, coronary angiogram, magnetic resonance imagery, nuclear imaging, CT scan, myocardial perfusion imagery, or electrocardiogram, genetic analysis, *e.g.*, identification of additional polymorphisms, *e.g.*, which contribute to the same disease, familial health history analysis, lifestyle analysis, or exercise stress tests, either alone or in combination. Furthermore, the diagnostic information obtained using the diagnostic assays described herein (singly or in combination with information of another genetic defect which contributes to the same disease, *e.g.*, a vascular disease or disorder), may be used to identify which subject will benefit from a particular clinical course of therapy useful for preventing, treating, ameliorating, or prolonging onset of the particular vascular disease or disorder in the particular subject. Clinical courses of therapy include, but are not limited to, administration of medication, non-surgical

intervention, surgical procedure or intervention, and use of surgical and non-surgical devices used in the treatment of vascular disease, such as, for example, stents or defibrillators.

Alternatively, the information, singly, or in combination with information of another genetic defect which contributes to the same disease, *e.g.,* a vascular disease or disorder, can be used prognostically for predicting whether a non-symptomatic subject is likely to develop a disease or condition which is associated with one or more specific alleles of PLCG1 or PAI-2 polymorphic regions in a subject. Based on the prognostic information, a health care provider can recommend a particular further diagnostic evaluation which will benefit the subject, or a particular clinical course of therapy, as described above.

In addition, knowledge of the identity of a particular PLCG1 or PAI-2 allele in a subject (the PLCG1 or PAI-2 genetic profile), singly, or preferably, in combination, allows customization of further diagnostic evaluation and/or a clinical course of therapy for a particular disease. For example, a subject's PLCG1 or PAI-2 genetic profile or the genetic profile of a disease or disorder associated with a specific allele of a PLCG1 or PAI-2 polymorphic region, *e.g.,* a vascular disease or disorder, can enable a health care provider: 1) to more efficiently and cost-effectively identify means for further diagnostic evaluation, including, but not limited to, further genetic analysis, familial health history analysis, or use of vascular imaging devices; 2) to more effectively prescribe a drug that will address the molecular basis of the disease or condition; 3) to more efficiently and cost-effectively identify an appropriate clinical course of therapy, including, but not limited to, lifestyle changes, medications, surgical or non-surgical devices, surgical or non-surgical intervention, or any combination thereof; and 4) to better determine the appropriate dosage of a particular drug or duration of a particular course of clinical therapy. For example, the expression level of PLCG1 or PAI-2 proteins, alone or in conjunction with the expression level of other genes, known to contribute to the same disease, can be measured in many subjects at various stages of the disease to generate a transcriptional or expression profile of the disease. Expression patterns of individual

subjects can then be compared to the expression profile of the disease to determine the appropriate drug, dose to administer to the subject, or course of clinical therapy.

The ability to target populations expected to show the highest clinical benefit, based on the PLCG1 or PAI-2 or disease genetic profile, can enable: 1) the repositioning of marketed drugs, surgical devices for use in treating, preventing, or ameliorating vascular diseases or disorders, or diagnostics, such as vascular imaging devices, with disappointing market results; 2) the rescue of drug candidates whose clinical development has been discontinued as a result of safety or efficacy limitations, which are subject subgroup-specific; 3) an accelerated and less costly development for drug candidates and more optimal drug labeling (*e.g.*, since the use of PLCG1 or PAI-2 as a marker is useful for optimizing effective dose); and 4) an accelerated, less costly, and more effective selection of a particular course of clinical therapy suited to a particular subject.

These and other methods are described in further detail in the following sections.

A. Prognostic and Diagnostic Assays

The present methods provide means for determining if a subject is or is not at risk of developing a disease, condition or disorder that is associated a specific PLCG1 or PAI-2 allele, *e.g.*, a vascular disease or a disease or disorder resulting therefrom.

The present invention provides methods for determining the molecular structure of a PLCG1 or PAI-2 gene, such as a human PLCG1 or PAI-2 gene, or a portion thereof. In one embodiment, determining the molecular structure of at least a portion of a PLCG1 or PAI-2 gene comprises determining the identity of an allelic variant of at least one polymorphic region of a PLCG1 or PAI-2 gene (determining the presence or absence of one or more of the allelic variants, or their complements, of SEQ ID NO:5 and/or SEQ ID NO:6). A polymorphic region of a PLCG1 or PAI-2 gene can be located in an exon, an intron, at an intron/exon border, or in the 5' upstream regulatory element of the PLCG1 or PAI-2 gene.

The invention provides methods for determining whether a subject is or is not at risk of developing a disease or disorder associated with a specific allelic variant of a polymorphic region of a PLCG1 or PAI-2 gene. Such diseases can be associated with aberrant PLCG1 or PAI-2 activity, *e.g.*, a vascular disease or disorder such as CAD or MI.

Analysis of one or more PLCG1 or PAI-2 polymorphic regions in a subject can be useful for predicting whether a subject is or is not likely to develop a vascular disease or disorder, *e.g.*, atherosclerosis, CAD, MI, ischemia, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism.

In preferred embodiments, the methods of the invention can be characterized as comprising detecting, in a sample of cells from the subject, the presence or absence of a specific allelic variant of one or more polymorphic regions of a PLCG1 or PAI-2 gene. Preferably, the presence of the variant allele of the PLCG1 gene and/or the reference allele of the PAI-2 gene described herein are detected. The allelic differences can be: (i) a difference in the identity of at least one nucleotide or (ii) a difference in the number of nucleotides, which difference can be a single nucleotide or several nucleotides. The invention also provides methods for detecting differences in PLCG1 or PAI-2 genes such as chromosomal rearrangements, *e.g.*, chromosomal dislocation. The invention can also be used in prenatal diagnostics.

A preferred detection method is allele specific hybridization using probes overlapping the polymorphic site and having about 5, 10, 20, 25, or 30 nucleotides around the polymorphic region. In a preferred embodiment of the invention, several probes capable of hybridizing specifically to allelic variants are attached to a solid phase support, *e.g.*, a "chip". Oligonucleotides can be bound to a solid support by a variety of processes, including lithography. For example a chip can hold up to 250,000 oligonucleotides (GeneChip, Affymetrix™). Mutation detection analysis using these chips comprising oligonucleotides, also termed "DNA probe arrays" is described *e.g.*, in Cronin *et al.* (1996) Human Mutation 7:244. In one embodiment, a chip comprises all

the allelic variants of at least one polymorphic region of a gene. The solid phase support is then contacted with a test nucleic acid and hybridization to the specific probes is detected. Accordingly, the identity of numerous allelic variants of one or more genes can be identified in a simple hybridization experiment. For example, the identity of the allelic variant of the nucleotide polymorphism in the 5' upstream regulatory element can be determined in a single hybridization experiment.

In other detection methods, it is necessary to first amplify at least a portion of a PLCG1 or PAI-2 gene prior to identifying the allelic variant. Amplification can be performed, *e.g.*, by PCR and/or LCR (see Wu and Wallace (1989) *Genomics* 4:560), according to methods known in the art. In one embodiment, genomic DNA of a cell is exposed to two PCR primers and amplification for a number of cycles sufficient to produce the required amount of amplified DNA. In preferred embodiments, the primers are located between 150 and 350 base pairs apart.

Alternative amplification methods include: self sustained sequence replication (Guatelli, J.C. *et al.*, (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh, D.Y. *et al.*, (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi, P.M. *et al.*, (1988) *Bio/Technology* 6:1197), and self-sustained sequence replication (*Guatelli et al.*, (1989) *Proc. Nat. Acad. Sci.* 87:1874), and nucleic acid based sequence amplification (NABSA), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In one embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence at least a portion of a PLCG1 or PAI-2 gene and detect allelic variants, *e.g.*, mutations, by comparing the sequence of the sample sequence with the corresponding reference (control) sequence. Exemplary sequencing reactions include those based on techniques developed by Maxam and Gilbert (*Proc. Natl Acad Sci USA* (1977) 74:560) or Sanger (Sanger *et al.* (1977) *Proc. Nat. Acad. Sci* 74:5463). It is also

contemplated that any of a variety of automated sequencing procedures may be utilized when performing the subject assays (*Biotechniques* (1995) 19:448), including sequencing by mass spectrometry (see, for example, U.S. Patent Number 5,547,835 and international patent application Publication Number WO 94/16101, entitled *DNA Sequencing by Mass Spectrometry* by H. Köster; U.S. Patent Number 5,547,835 and international patent application Publication Number WO 94/21822 entitled "DNA Sequencing by Mass Spectrometry Via Exonuclease Degradation" by H. Köster), and U.S Patent Number 5,605,798 and International Patent Application No. PCT/US96/03651 entitled *DNA Diagnostics Based on Mass Spectrometry* by H. Köster;. Cohen *et al.* (1996) *Adv Chromatogr* 36:127-162; and Griffin *et al.* (1993) *Appl Biochem Biotechnol* 38:147-159). It will be evident to one skilled in the art that, for certain embodiments, the occurrence of only one, two or three of the nucleic acid bases need be determined in the sequencing reaction. For instance, A-track or the like, *e.g.*, where only one nucleotide is detected, can be carried out.

Yet other sequencing methods are disclosed, *e.g.*, in U.S. Patent Number 5,580,732 entitled "Method of DNA sequencing employing a mixed DNA-polymer chain probe" and U.S. Patent Number 5,571,676 entitled "Method for mismatch-directed *in vitro* DNA sequencing."

In some cases, the presence of a specific allele of a PLCG1 or PAI-2 gene in DNA from a subject can be shown by restriction enzyme analysis. For example, a specific nucleotide polymorphism can result in a nucleotide sequence comprising a restriction site which is absent from the nucleotide sequence of another allelic variant.

In a further embodiment, protection from cleavage agents (such as a nuclease, hydroxylamine or osmium tetroxide and with piperidine) can be used to detect mismatched bases in RNA/RNA DNA/DNA, or RNA/DNA heteroduplexes (Myers, *et al.* (1985) *Science* 230:1242). In general, the technique of "mismatch cleavage" starts by providing heteroduplexes formed by hybridizing a control nucleic acid, which is optionally labeled, *e.g.*, RNA or DNA, comprising a nucleotide sequence of a PLCG1 or PAI-2 allelic variant with a sample nucleic acid, *e.g.*, RNA or DNA, obtained from a

tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as duplexes formed based on basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S1 nuclease to enzymatically digest the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine whether the control and sample nucleic acids have an identical nucleotide sequence or in which nucleotides they are different. See, for example, Cotton *et al* (1988) *Proc. Natl Acad Sci USA* 85:4397; Saleeba *et al* (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control or sample nucleic acid is labeled for detection.

In another embodiment, an allelic variant can be identified by denaturing high-performance liquid chromatography (DHPLC) (Oefner and Underhill, (1995) *Am. J. Human Gen.* 57:Suppl. A266). DHPLC uses reverse-phase ion-pairing chromatography to detect the heteroduplexes that are generated during amplification of PCR fragments from individuals who are heterozygous at a particular nucleotide locus within that fragment (Oefner and Underhill (1995) *Am. J. Human Gen.* 57:Suppl. A266). In general, PCR products are produced using PCR primers flanking the DNA of interest. DHPLC analysis is carried out and the resulting chromatograms are analyzed to identify base pair alterations or deletions based on specific chromatographic profiles (see O'Donovan *et al.* (1998) *Genomics* 52:44-49).

In other embodiments, alterations in electrophoretic mobility is used to identify the type of PLCG1 or PAI-2 allelic variant. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita *et al.* (1989) *Proc Natl. Acad. Sci USA* 86:2766, see also Cotton (1993) *Mutat Res* 285:125-144; and Hayashi (1992) *Genet Anal Tech Appl* 9:73-79). Single-stranded DNA fragments of sample and control nucleic

acids are denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In another preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen *et al.* (1991) *Trends Genet* 7:5).

In yet another embodiment, the identity of an allelic variant of a polymorphic region is obtained by analyzing the movement of a nucleic acid comprising the polymorphic region in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers *et al.* (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing agent gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys Chem* 265:1275).

Examples of techniques for detecting differences of at least one nucleotide between 2 nucleic acids include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide probes may be prepared in which the known polymorphic nucleotide is placed centrally (allele-specific probes) and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki *et al.* (1986) *Nature* 324:163); Saiki *et al* (1989) *Proc. Natl Acad. Sci USA* 86:6230; and Wallace *et al.* (1979) *Nucl. Acids Res.* 6:3543). Such allele specific oligonucleotide hybridization techniques may be used for the simultaneous detection of several nucleotide changes in different polylmorphic regions of PLCG1 or PAI-2. For example, oligonucleotides having nucleotide sequences of specific allelic variants are attached to a

hybridizing membrane and this membrane is then hybridized with labeled sample nucleic acid. Analysis of the hybridization signal will then reveal the identity of the nucleotides of the sample nucleic acid.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the allelic variant of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs *et al* (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238; Newton *et al.* (1989) *Nucl. Acids Res.* 17:2503). This technique is also termed "PROBE" for Probe Oligo Base Extension. In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini *et al* (1992) *Mol. Cell Probes* 6:1).

In another embodiment, identification of the allelic variant is carried out using an oligonucleotide ligation assay (OLA), as described, *e.g.,* in U.S. Patent Number 4,998,617 and in Landegren, U. *et al.*, (1988) *Science* 241:1077-1080. The OLA protocol uses two oligonucleotides which are designed to be capable of hybridizing to abutting sequences of a single strand of a target. One of the oligonucleotides is linked to a separation marker, e.g,. biotinylated, and the other is detectably labeled. If the precise complementary sequence is found in a target molecule, the oligonucleotides will hybridize such that their termini abut, and create a ligation substrate. Ligation then permits the labeled oligonucleotide to be recovered using avidin, or another biotin ligand. Nickerson, D. A. *et al.* have described a nucleic acid detection assay that combines attributes of PCR and OLA (Nickerson, D. A. *et al.*, (1990) *Proc. Natl. Acad. Sci. (U.S.A.)* 87:8923-8927. In this method, PCR is used to achieve the exponential amplification of target DNA, which is then detected using OLA.

Several techniques based on this OLA method have been developed and can be used to detect specific allelic variants of a polymorphic region of a PLCG1 or PAI-2 gene. For example, U.S. Patent Number 5,593,826 discloses an OLA using an oligonucleotide having 3'-amino group and a 5'-phosphorylated oligonucleotide to form a conjugate having a phosphoramidate linkage. In another variation of OLA described in Tobe *et al.* ((1996) *Nucleic Acids Res* 24: 3728), OLA combined with PCR permits typing of two alleles in a single microtiter well. By marking each of the allele-specific primers with a unique hapten, *i.e.* digoxigenin and fluorescein, each OLA reaction can be detected by using hapten specific antibodies that are labeled with different enzyme reporters, alkaline phosphatase or horseradish peroxidase. This system permits the detection of the two alleles using a high throughput format that leads to the production of two different colors.

The invention further provides methods for detecting single nucleotide polymorphisms in a PLCG1 or PAI-2 gene. Because single nucleotide polymorphisms constitute sites of variation flanked by regions of invariant sequence, their analysis requires no more than the determination of the identity of the single nucleotide present at the site of variation and it is unnecessary to determine a complete gene sequence for each subject. Several methods have been developed to facilitate the analysis of such single nucleotide polymorphisms.

In one embodiment, the single base polymorphism can be detected by using a specialized exonuclease-resistant nucleotide, as disclosed, *e.g.*, in Mundy, C. R. (U.S. Patent Number 4,656,127). According to the method, a primer complementary to the allelic sequence immediately 3' to the polymorphic site is permitted to hybridize to a target molecule obtained from a particular animal or human. If the polymorphic site on the target molecule contains a nucleotide that is complementary to the particular exonuclease-resistant nucleotide derivative present, then that derivative will be incorporated onto the end of the hybridized primer. Such incorporation renders the primer resistant to exonuclease, and thereby permits its detection. Since the identity of the exonuclease-resistant derivative of the sample is known, a finding that the primer has

become resistant to exonucleases reveals that the nucleotide present in the polymorphic site of the target molecule was complementary to that of the nucleotide derivative used in the reaction. This method has the advantage that it does not require the determination of large amounts of extraneous sequence data.

In another embodiment of the invention, a solution-based method is used for determining the identity of the nucleotide of a polymorphic site. Cohen, D. *et al.* (French Patent 2,650,840; PCT Appln. No. WO91/02087). As in the Mundy method of U.S. Patent Number 4,656,127, a primer is employed that is complementary to allelic sequences immediately 3' to a polymorphic site. The method determines the identity of the nucleotide of that site using labeled dideoxynucleotide derivatives, which, if complementary to the nucleotide of the polymorphic site will become incorporated onto the terminus of the primer.

An alternative method, known as Genetic Bit Analysis or GBA™ is described by Goelet, P. *et al.* (PCT Appln. No. 92/15712). The method of Goelet, P. *et al.* uses mixtures of labeled terminators and a primer that is complementary to the sequence 3' to a polymorphic site. The labeled terminator that is incorporated is thus determined by, and complementary to, the nucleotide present in the polymorphic site of the target molecule being evaluated. In contrast to the method of Cohen *et al.* (French Patent 2,650,840; PCT Appln. No. WO91/02087) the method of Goelet, P. *et al.* is preferably a heterogeneous phase assay, in which the primer or the target molecule is immobilized to a solid phase.

Recently, several primer-guided nucleotide incorporation procedures for assaying polymorphic sites in DNA have been described (Komher, J. S. *et al.*, (1989) *Nucl. Acids. Res.* 17:7779-7784; Sokolov, B. P., (1990) *Nucl. Acids Res.* 18:3671; Syvanen, A. -C., *et al.*, (1990) *Genomics* 8:684-692; Kuppuswamy, M. N. *et al.*, (1991) *Proc. Natl. Acad. Sci. (U.S.A.)* 88:1143-1147; Prezant, T. R. *et al.*, (1992) *Hum. Mutat.* 1:159-164; Ugozzoli, L. *et al.*, (1992) *GATA* 9:107-112; Nyren, P. (1993) *et al.*, *Anal. Biochem.* 208:171-175). These methods differ from GBA™ in that they all rely on the incorporation of labeled deoxynucleotides to discriminate between bases at a polymorphic site. In such a format, since the signal is proportional to the number of

deoxynucleotides incorporated, polymorphisms that occur in runs of the same nucleotide can result in signals that are proportional to the length of the run (Syvanen, A.C., *et al.*, (1993) *Amer. J. Hum. Genet.* 52:46-59).

For determining the identity of the allelic variant of a polymorphic region located in the coding region of a PLCG1 or PAI-2 gene, yet other methods than those described above can be used. For example, identification of an allelic variant which encodes a mutated PLCG1 or PAI-2 protein can be performed by using an antibody specifically recognizing the mutant protein in, *e.g.*, immunohistochemistry or immunoprecipitation. Antibodies to wild-type PAI-2 proteins are described in, for example, Tsuchiya, *et al.* (1995) *Gen Diagnos Pathol* 141(1):41. Antibodies to wild-type PLCG1 are described in, for example, Smith, *et al.* (1994) *Proc. Natl. Acad. Sci.* 91(14):6554. Other antibodies to wild-type PLCG1 or PAI-2 or mutated forms of PLCG1 or PAI-2 proteins can be prepared according to methods known in the art.

Alternatively, one can also measure an activity of a PLCG1 or PAI-2 protein, such as binding to a PLCG1 or PAI-2 ligand. Binding assays are known in the art and involve, *e.g.*, obtaining cells from a subject, and performing binding experiments with a labeled ligand, to determine whether binding to the mutated form of the protein differs from binding to the wild-type of the protein.

Antibodies directed against reference or mutant PLCG1 or PAI-2 polypeptides or allelic variant thereof, which are discussed above, may also be used in disease diagnostics and prognostics. Such diagnostic methods, may be used to detect abnormalities in the level of PLCG1 or PAI-2 polypeptide expression, or abnormalities in the structure and/or tissue, cellular, or subcellular location of a PLCG1 or PAI-2 polypeptide. Structural differences may include, for example, differences in the size, electronegativity, or antigenicity of the mutant PLCG1 or PAI-2 polypeptide relative to the normal PLCG1 or PAI-2 polypeptide. Protein from the tissue or cell type to be analyzed may easily be detected or isolated using techniques which are well known to one of skill in the art, including but not limited to Western blot analysis. For a detailed explanation of methods for carrying out Western blot analysis, see Sambrook *et al*, 1989,

supra, at Chapter 18. The protein detection and isolation methods employed herein may also be such as those described in Harlow and Lane, for example, (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety.

This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody (see below) coupled with light microscopic, flow cytometric, or fluorimetric detection. The antibodies (or fragments thereof) useful in the present invention may, additionally, be employed histologically, as in immunofluorescence or immunoelectron microscopy, for *in situ* detection of PLCG1 or PAI-2 polypeptides. *In situ* detection may be accomplished by removing a histological specimen from a subject, and applying thereto a labeled antibody of the present invention. The antibody (or fragment) is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the PLCG1 or PAI-2 polypeptide, but also its distribution in the examined tissue. Using the present invention, one of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such *in situ* detection.

Often a solid phase support or carrier is used as a support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the

art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

One means for labeling an anti-PLCG1 or PAI-2 polypeptide specific antibody is via linkage to an enzyme and use in an enzyme immunoassay (EIA) (Voller, "The Enzyme Linked Immunosorbent Assay (ELISA)", *Diagnostic Horizons* 2:1-7, 1978, Microbiological Associates Quarterly Publication, Walkersville, MD; Voller, et al., (1978) J. Clin. Pathol. 31:507-520; Butler, (1981) *Meth. Enzymol.* 73:482-523; Maggio, (ed.) *Enzyme Immunoassay*, CRC Press, Boca Raton, FL, 1980; Ishikawa, *et al.*, (eds.) *Enzyme Immunoassay*, Kgaku Shoin, Tokyo, 1981). The enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. The detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect fingerprint gene wild type or mutant peptides through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., *Principles of Radioimmunoassays*, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by such means as the use of a gamma counter or a scintillation counter or by autoradiography.

It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine.

The antibody can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

If a polymorphic region is located in an exon, either in a coding or non-coding portion of the gene, the identity of the allelic variant can be determined by determining the molecular structure of the mRNA, pre-mRNA, or cDNA. The molecular structure can be determined using any of the above described methods for determining the molecular structure of the genomic DNA.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits, such as those described above, comprising at least one probe or primer nucleic acid described herein, which may be conveniently used, *e.g.*, to determine

whether a subject is or is not at risk of developing a disease associated with a specific PLCG1 or PAI-2 allelic variant.

Sample nucleic acid to be analyzed by any of the above-described diagnostic and prognostic methods can be obtained from any cell type or tissue of a subject. For example, a subject's bodily fluid (*e.g.* blood) can be obtained by known techniques (*e.g.* venipuncture). Alternatively, nucleic acid tests can be performed on dry samples (*e.g.* hair or skin). Fetal nucleic acid samples can be obtained from maternal blood as described in International Patent Application No. WO91/07660 to Bianchi. Alternatively, amniocytes or chorionic villi may be obtained for performing prenatal testing.

Diagnostic procedures may also be performed *in situ* directly upon tissue sections (fixed and/or frozen) of subject tissue obtained from biopsies or resections, such that no nucleic acid purification is necessary. Nucleic acid reagents may be used as probes and/or primers for such *in situ* procedures (see, for example, Nuovo, G.J., 1992, PCR *in situ* hybridization: protocols and applications, Raven Press, NY).

In addition to methods which focus primarily on the detection of one nucleic acid sequence, profiles may also be assessed in such detection schemes. Fingerprint profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR.

B. Pharmacogenomics

Knowledge of the identity of the allele of one or more PLCG1 gene or PAI-2 gene polymorphic regions in a subject (the PLCG1 and/or PAI-2 genetic profile), alone or in conjunction with information of other genetic defects associated with the same disease (the genetic profile of the particular disease) also allows selection and customization of the therapy, *e.g.*, a particular clinical course of therapy and/or further diagnostic evaluation for a particular disease to the subject's genetic profile. For example, subjects having a specific allele of a PLCG1 or PAI-2 gene, singly or in combination, may or may not exhibit symptoms of a particular disease or be predisposed

to developing symptoms of a particular disease. Further, if those subjects are symptomatic, they may or may not respond to a certain drug, *e.g.*, a specific therapeutic used in the treatment or prevention of a vascular disease or disorder, *e.g.*, CAD or MI, such as beta blocker drugs, calcium channel blocker drugs, or nitrate drugs, but may respond to another. Furthermore, they may or may not respond to other treatments, including, for example, use of devices for treatment of vascular disease, or surgical and/or non-surgical courses of treatment. Moreover, if a subject does or does not exhibit symptoms of a particular disease, the subject may or may not benefit from further diagnostic evaluation, including, for example, use of vascular imaging devices. Thus, generation of a PLCG1 or PAI-2 genetic profile, (*e.g.*, categorization of alterations in PLCG1 or PAI-2 genes which are associated with the development of a particular disease), from a population of subjects, who are symptomatic for a disease or condition that is caused by or contributed to by a defective and/or deficient PLCG1 or PAI-2 gene and/or protein (a PLCG1 or PAI-2 genetic population profile) and comparison of a subject's PLCG1 or PAI-2 profile to the population profile, permits the selection or design of drugs that are expected to be safe and efficacious for a particular subject or subject population (*i.e.*, a group of subjects having the same genetic alteration), as well as the selection or design of a particular clinical course of therapy or further diagnostic evaluations that are expected to be safe and efficacious for a particular subject or subject population.

For example, a PLCG1 or PAI-2 population profile can be performed by determining the PLCG1 or PAI-2 profile, *e.g.*, the identity of PLCG1 or PAI-2 alleles, in a subject population having a disease, which is associated with one or more specific alleles of PLCG1 or PAI-2 polymorphic regions. Optionally, the PLCG1 or PAI-2 population profile can further include information relating to the response of the population to a PLCG1 or PAI-2 therapeutic, using any of a variety of methods, including, monitoring: 1) the severity of symptoms associated with the PLCG1 or PAI-2 related disease; 2) PLCG1 or PAI-2 gene expression level; 3) PLCG1 or PAI-2 mRNA level; and/or 4) PLCG1 or PAI-2 protein level, and dividing or categorizing the

population based on particular PLCG1 or PAI-2 alleles. The PLCG1 or PAI-2 genetic population profile can also, optionally, indicate those particular PLCG1 or PAI-2 alleles which are present in subjects that are either responsive or non-responsive to a particular therapeutic, clinical course of therapy, or diagnostic evaluation. This information or population profile, is then useful for predicting which individuals should respond to particular drugs, particular clinical courses of therapy, or diagnostic evaluations based on their individual PLCG1 or PAI-2 genetic profile.

In a preferred embodiment, the PLCG1 or PAI-2 profile is a transcriptional or expression level profile and is comprised of determining the expression level of PLCG1 or PAI-2 proteins, alone or in conjunction with the expression level of other genes known to contribute to the same disease at various stages of the disease.

Pharmacogenomic studies can also be performed using transgenic animals. For example, one can produce transgenic mice, *e.g.,* as described herein, which contain a specific allelic variant of a PLCG1 or PAI-2 gene. These mice can be created, e.g, by replacing their wild-type PLCG1 or PAI-2 gene with an allele of the human PLCG1 or PAI-2 gene. The response of these mice to specific PLCG1 or PAI-2 particular therapeutics, clinical courses of treatment, and/or diagnostic evaluations can then be determined.

(i) Diagnostic Evaluation

In one embodiment, the polymorphisms of the present invention are used to determine the most appropriate diagnostic evaluation and to determine whether or not a subject will benefit from further diagnostic evaluation. For example, if a subject has two copies of a thymidine allele at nucleotide position 170871 of the PAI-2 gene, or the complement thereof, and two copies of a thymidine allele at nucleotide position 11345540 of the PLCG1 gene, or the complement thereof, that subject is approximately 3-fold less likely to develop a vascular disease such as CAD or MI as compared to a subject having any other combination of alleles at those loci, and therefore would be less

likely to require or benefit from further diagnostic evaluation for a vascular disease or disorder.

Thus, in one embodiment, the invention provides methods for classifying a subject who or is or is not at risk for developing, a vascular disease or disorder as a candidate for further diagnostic evaluation for a vascular disease or disorder comprising the steps of determining the PLCG1 and/or PAI-2 genetic profile of the subject, comparing the subject's PLCG1 and/or PAI-2 genetic profile to a PLCG1 genetic population profile and/or a PAI-2 genetic population profile, and classifying the subject based on the identified genetic profiles as a subject who is a candidate for further diagnostic evaluation for a vascular disease or disorder.

In one embodiment, the subject's PLCG1 and/or PAI-2 genetic profile is determined by identifying the nucleotide present at nucleotide position 11345540 of SEQ ID NO:1 and/or the nucleotide present at nucleotide position 170871 of SEQ ID NO:3. The subject's genetic profile can also be determined by identifying the amino acid present at amino acid position 813 of SEQ ID NO:2 and/or the amino acid residue present at position 120 of SEQ ID NO:4. Methods of further diagnostic evaluation include use of vascular imaging devices such as, for example, angiography, cardiac ultrasound, coronary angiogram, magnetic resonance imagery, nuclear imaging, CT scan, myocardial perfusion imagery, or electrocardiogram, or may include genetic analysis, familial health history analysis, lifestyle analysis, exercise stress tests, or any combination thereof.

In another embodiment, the invention provides methods for selecting an effective vascular imaging device as a diagnostic tool for a vascular disease or disorder comprising the steps of determining the PLCG1 and/or PAI-2 genetic profile of the subject; comparing the subject's PLCG1 and/or PAI-2 genetic profile to a PLCG1 genetic population profile and/or a PAI-2 genetic population profile; and selecting an effective vascular imaging device as a diagnostic tool for a vascular disease or disorder. In a preferred embodiment, the vascular imaging device is selected from the group consisting of angiography, cardiac ultrasound, coronary angiogram, magnetic resonance imagery, nuclear imaging, CT scan, myocardial perfusion imagery, electrocardiogram, or

any combination thereof.

(ii) Clinical Course of Therapy

In another aspect, the polymorphisms of the present invention are used to determine the most appropriate clinical course of therapy for a subject who is at risk of a vascular disease or disorder, and will aid in the determination of whether the subject will benefit from such clinical course of therapy, as determined by identification of one, or preferably, both of the polymorphisms of the invention.

In one aspect, the invention relates to the SNPs identified as described herein, both singly and, preferably, in combination, as well as to the use of these SNPs, and others in these genes, particularly those nearby in linkage disequilibrium with these SNPs, both singly and, preferably, in combination, for prediction of a particular clinical course of therapy for a subject who has, or is or is not at risk for developing, a vascular disease. In one embodiment, the invention provides a method for determining whether a subject will or will not benefit from a particular course of therapy by determining the presence of one, or preferably both, of the identities of the polymorphisms of the invention. For example, the determination of the polymorphisms of the invention, singly, or in combination, will aid in the determination of whether an individual will benefit from surgical revascularization and/or will benefit by the implantation of a stent following surgical revascularization, and will aid in the determination of the likelihood of success or failure of a particular clinical course of therapy.

For example, if a subject has two copies of a thymidine allele at nucleotide position 170871 of the PAI-2 gene, or the complement thereof, and two copies of a thymidine allele at nucleotide position 11345540 of the PLCG1 gene, or the complement thereof, that subject is approximately 3-fold less likely to develop a vascular disease such as CAD or MI as compared to a subject having any other combination of alleles at those loci. Therefore, that subject would be less likely to require or benefit from any clinical course of therapy.

An appropriate clinical course of therapy for a vascular disease or disorder may include, for example, a lifestyle change, including, for example, a change in diet or environment. Other clinical courses of therapy include, but are not limited to, use of surgery or surgical devices. Surgical therapy for the treatment of vascular disorders, includes, for example, surgical revascularization, such as angioplasty, *e.g.*, percutaneous transluminal coronary balloon angioplasty (PTCA), or laser angioplasty, or coronary bypass grafting (CABG). Surgical devices used in the treatment or prevention of vascular diseases or disorders, include, for example, devices used in angioplasty, such as balloon angioplasty or laser angioplasty, or implantation of a stent, or any combination thereof.

C. Monitoring Effects of PLCG1 or PAI-2 Therapeutics During Clinical Trials

The present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate identified, *e.g.*, by the screening assays described herein) comprising the steps of (i) obtaining a preadministration sample from a subject prior to administration of the agent; (ii) detecting the level of expression or activity of a PLCG1 or PAI-2 protein, mRNA or gene in the preadministration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the PLCG1 or PAI-2 protein, mRNA or gene in the post-administration samples; (v) comparing the level of expression or activity of the PLCG1 or PAI-2 protein, mRNA, or gene in the preadministration sample with those of the PLCG1 or PAI-2 protein, mRNA, or gene in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of PLCG1 or PAI-2 to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of PLCG1 or PAI-2 to lower levels than detected, *i.e.*, to decrease the effectiveness of the agent.

Cells of a subject may also be obtained before and after administration of a PLCG1 or PAI-2 therapeutic to detect the level of expression of genes other than PLCG1 or PAI-2, to verify that the PLCG1 or PAI-2 therapeutic does not increase or decrease the expression of genes which could be deleterious. This can be done, *e.g.*, by using the method of transcriptional profiling. Thus, mRNA from cells exposed *in vivo* to a PLCG1 or PAI-2 therapeutic and mRNA from the same type of cells that were not exposed to the PLCG1 or PAI-2 therapeutic could be reverse transcribed and hybridized to a chip containing DNA from numerous genes, to thereby compare the expression of genes in cells treated and not treated with a PLCG1 or PAI-2 therapeutic. If, for example a PLCG1 or PAI-2 therapeutic turns on the expression of a proto-oncogene in a subject, use of this particular PLCG1 or PAI-2 therapeutic may be undesirable.

D. Methods of Treatment

The present invention provides for both prophylactic and therapeutic methods of treating a subject having or likely to develop a disorder associated with specific PLCG1 or PAI-2 alleles and/or aberrant PLCG1 or PAI-2 expression or activity, *e.g.*, vascular diseases or disorders.

i) Prophylactic Methods

In one aspect, the invention provides a method for preventing a disease or disorder associated with a specific PLCG1 or PAI-2 allele such as a vascular disease or disorder, *e.g.*, CAD or MI, and medical conditions resulting therefrom, by administering to the subject an agent which counteracts the unfavorable biological effect of the specific PLCG1 or PAI-2 allele. Subjects at risk, or at a lesser than normal risk, for such a disease can be identified by a diagnostic or prognostic assay, *e.g.*, as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms associated with specific PLCG1 or PAI-2 alleles, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending on the identity of the PLCG1 or PAI-2 allele in a subject, a compound that counteracts the effect of this allele

is administered. The compound can be a compound modulating the activity of PLCG1 or PAI-2, *e.g.*, a PLCG1 or PAI-2 inhibitor. The treatment can also be a specific lifestyle change, *e.g.*, a change in diet or an environmental alteration. In particular, the treatment can be undertaken prophylactically, before any other symptoms are present. Such a prophylactic treatment could thus prevent the development of aberrant vascular activity, *e.g.*, the production of atherosclerotic plaque leading to, *e.g.*, CAD or MI. The prophylactic methods are similar to therapeutic methods of the present invention and are further discussed in the following subsections.

(ii) Therapeutic Methods

The invention further provides methods of treating a subject having a disease or disorder associated with a specific allelic variant of a polymorphic region of a PLCG1 or PAI-2 gene. Preferred diseases or disorders include vascular diseases and disorders, and disorders resulting therefrom (*e.g.*, such as, for example, atherosclerosis, CAD, MI, ischemia, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism).

In one embodiment, the method comprises (a) determining the identity of an allelic variant of a PLCG1 gene, a PAI-2 gene, or preferably, the identities of both; and (b) administering to the subject a compound that compensates for the effect of the specific allelic variant(s). The polymorphic region can be localized at any location of the gene, *e.g.*, in a regulatory element (*e.g.*, in a 5' upstream regulatory element), in an exon, (*e.g.*, coding region of an exon), in an intron, or at an exon/intron border. Thus, depending on the site of the polymorphism in the PLCG1 or PAI-2 gene, a subject having a specific variant of the polymorphic region which is associated with a specific disease or condition, can be treated with compounds which specifically compensate for the effect of the allelic variant.

In a preferred embodiment, the identity of one or more of the following nucleotides of a PLCG1 or PAI-2 gene of a subject is determined: a thymidine in the PLCG1 gene at residue 64001 of the reference sequence GI 11345540 (polymorphism

ID No. G523u1), or the complement thereof, or a thymidine at residue 170871 of the reference sequence GI 6705901 (polymorphism ID No. PAI2u1), or the complement thereof. In a preferred embodiment, the identities of both nucleotides is determined.

If a subject has two copies of the variant allele of the PLCG1 gene (*e.g.*, thymidine in the PLCG1 gene at residue 64001 of the reference sequence GI 11345540), or the complement thereof, and two copies of the reference allele of the PAI-2 gene (*e.g.*, thymidine at residue 170871 of the reference sequence GI 6705901), or the complement thereof, as set forth in Table 3, that subject is at a lesser than normal risk of developing a vascular disease such as CAD or MI.

Generally, the allelic variant can be a mutant allele, *i.e.*, an allele which when present in one, or preferably two copies, in a subject results in a change in the phenotype of the subject. A mutation can be a substitution, deletion, and/or addition of at least one nucleotide relative to the wild-type allele (*i.e.*, the reference sequence). Depending on where the mutation is located in the PLCG1 or PAI-2 gene, the subject can be treated to specifically compensate for the mutation. For example, if the mutation is present in the coding region of the gene and results in a more active PLCG1 or PAI-2 protein, the subject can be treated, *e.g.*, by administration to the subject of a medication or course of clinical treatment which treat, prevents, or ameliorates a vascular disease or disorder. Normal PLCG1 or PAI-2 protein can also be used to counteract or compensate for the endogenous mutated form of the PLCG1 or PAI-2 protein. Normal PLCG1 or PAI-2 protein can be directly delivered to the subject or indirectly by gene therapy wherein some cells in the subject are transformed or transfected with an expression construct encoding wild-type PLCG1 or PAI-2 protein. Nucleic acids encoding reference human PLCG1 or PAI-2 protein are set forth in SEQ ID NOs.:1 and 3, respectively (GI Accession Nos. 11345540 and 6705901).

Yet in another embodiment, the invention provides methods for treating a subject having a mutated PLCG1 or PAI-2 gene, in which the mutation is located in a regulatory region of the gene. Such a regulatory region can be localized in the 5' upstream regulatory element of the gene, in the 5' or 3' untranslated region of an exon, or

in an intron. A mutation in a regulatory region can result in increased production of PLCG1 or PAI-2 protein, decreased production of PLCG1 or PAI-2 protein, or production of PLCG1 or PAI-2 having an aberrant tissue distribution. The effect of a mutation in a regulatory region upon the PLCG1 or PAI-2 protein can be determined, *e.g.*, by measuring the PLCG1 or PAI-2 protein level or mRNA level in cells having a PLCG1 or PAI-2 gene having this mutation and which, normally (*i.e.*, in the absence of the mutation) produce PLCG1 or PAI-2 protein. The effect of a mutation can also be determined *in vitro*. For example, if the mutation is in the 5' upstream regulatory element, a reporter construct can be constructed which comprises the mutated 5' upstream regulatory element linked to a reporter gene, the construct transfected into cells, and comparison of the level of expression of the reporter gene under the control of the mutated 5' upstream regulatory element and under the control of a wild-type 5' upstream regulatory element. Such experiments can also be carried out in mice transgenic for the mutated 5' upstream regulatory element. If the mutation is located in an intron, the effect of the mutation can be determined, *e.g.*, by producing transgenic animals in which the mutated PLCG1 or PAI-2 gene has been introduced and in which the wild-type gene may have been knocked out. Comparison of the level of expression of PLCG1 or PAI-2 in the mice transgenic for the mutant human PLCG1 or PAI-2 gene with mice transgenic for a wild-type human PLCG1 or PAI-2 gene will reveal whether the mutation results in increased, or decreased synthesis of the PLCG1 or PAI-2 protein and/or aberrant tissue distribution of PLCG1 or PAI-2 protein. Such analysis could also be performed in cultured cells, in which the human mutant PLCG1 or PAI-2 gene is introduced and, *e.g.*, replaces the endogenous wild-type PLCG1 or PAI-2 gene in the cell. Thus, depending on the effect of the mutation in a regulatory region of a PLCG1 or PAI-2 gene, a specific treatment can be administered to a subject having such a mutation. Accordingly, if the mutation results in increased PLCG1 or PAI-2 protein levels, the subject can be treated by administration of a compound which reduces PLCG1 or PAI-2 protein production, *e.g.*, by reducing PLCG1 or PAI-2 gene expression or a compound which inhibits or reduces the activity of PLCG1 or PAI-2.

A correlation between drug responses and specific alleles of PLCG1 or PAI-2 can be shown, for example, by clinical studies wherein the response to specific drugs of subjects having different allelic variants of a polymorphic region of a PLCG1 or PAI-2 gene is compared. Such studies can also be performed using animal models, such as mice having various alleles of human PLCG1 or PAI-2 genes and in which, *e.g.*, the endogenous PLCG1 or PAI-2 has been inactivated such as by a knock-out mutation. Test drugs are then administered to the mice having different human PLCG1 or PAI-2 alleles and the response of the different mice to a specific compound is compared. Accordingly, the invention provides assays for identifying the drug which will be best suited for treating a specific disease or condition in a subject. For example, it will be possible to select drugs which will be devoid of toxicity, or have the lowest level of toxicity possible for treating a subject having a disease or condition.

Other Uses For the Nucleic Acid Molecules of the Invention

The identification of different alleles of PLCG1 or PAI-2 can also be useful for identifying an individual among other individuals from the same species. For example, DNA sequences can be used as a fingerprint for detection of different individuals within the same species (Thompson, J. S. and Thompson, eds., Genetics in Medicine, WB Saunders Co., Philadelphia, PA (1991)). This is useful, for example, in forensic studies and paternity testing, as described below.

A. Forensics

Determination of which specific allele occupies a set of one or more polymorphic sites in an individual identifies a set of polymorphic forms that distinguish the individual from others in the population. *See generally* National Research Council, *The Evaluation of Forensic DNA Evidence* (Eds. Pollard *et al.*, National Academy Press, DC, 1996). The more polymorphic sites that are analyzed, the lower the probability that the set of polymorphic forms in one individual is the same as that in an unrelated individual. Preferably, if multiple sites are analyzed, the sites are unlinked. Thus, the

polymorphisms of the invention can be used in conjunction with known polymorphisms in distal genes. Preferred polymorphisms for use in forensics are biallelic because the population frequencies of two polymorphic forms can usually be determined with greater accuracy than those of multiple polymorphic forms at multi-allelic loci.

The capacity to identify a distinguishing or unique set of polymorphic markers in an individual is useful for forensic analysis. For example, one can determine whether a blood sample from a suspect matches a blood or other tissue sample from a crime scene by determining whether the set of polymorphic forms occupying selected polymorphic sites is the same in the suspect and the sample. If the set of polymorphic markers does not match between a suspect and a sample, it can be concluded (barring experimental error) that the suspect was not the source of the sample. If the set of markers is the same in the sample as in the suspect, one can conclude that the DNA from the suspect is consistent with that found at the crime scene. If frequencies of the polymorphic forms at the loci tested have been determined (*e.g.*, by analysis of a suitable population of individuals), one can perform a statistical analysis to determine the probability that a match of suspect and crime scene sample would occur by chance.

p(ID) is the probability that two random individuals have the same polymorphic or allelic form at a given polymorphic site. For example, in biallelic loci, four genotypes are possible: AA, AB, BA, and BB. If alleles A and B occur in a haploid genome of the organism with frequencies x and y, the probability of each genotype in a diploid organism is (see WO 95/12607):

Homozygote: $p(AA)= x^2$

Homozygote: $p(BB)= y^2 = (1-x)^2$

Single Heterozygote: $p(AB)= p(BA)= xy = x(1-x)$

Both Heterozygotes: $p(AB+BA)= 2xy = 2x(1-x)$

The probability of identity at one locus (*i.e.*, the probability that two individuals, picked at random from a population will have identical polymorphic forms at a given locus) is given by the equation: $p(ID) = (x^2)$.

These calculations can be extended for any number of polymorphic forms at a given locus. For example, the probability of identity p(ID) for a 3-allele system where the alleles have the frequencies in the population of x, y, and z, respectively, is equal to the sum of the squares of the genotype frequencies: $P(ID) = x^4 + (2xy)^2 + (2yz)^2 + (2xz)^2 + z^4 + y^4$.

In a locus of n alleles, the appropriate binomial expansion is used to calculate p(ID) and p(exc).

The cumulative probability of identity (cum p(ID)) for each of multiple unlinked loci is determined by multiplying the probabilities provided by each locus: cum p(ID) = p(ID1)p(ID2)p(ID3)...p(IDn).

The cumulative probability of non-identity for n loci (*i.e.,* the probability that two random individuals will be difference at 1 or more loci) is given by the equation: cum p(nonID) = 1-cum p(ID).

If several polymorphic loci are tested, the cumulative probability of non-identity for random individuals becomes very high (*e.g.,* one billion to one). Such probabilities can be taken into account together with other evidence in determining the guilt or innocence of the suspect.

B. Paternity Testing

The object of paternity testing is usually to determine whether a male is the father of a child. In most cases, the mother of the child is known, and thus, it is possible to trace the mother's contribution to the child's genotype. Paternity testing investigates whether the part of the child's genotype not attributable to the mother is consistent to that of the putative father. Paternity testing can be performed by analyzing sets of polymorphisms in the putative father and in the child.

If the set of polymorphisms in the child attributable to the father does not match the set of polymorphisms of the putative father, it can be concluded, barring experimental error, that that putative father is not the real father. If the set of polymorphisms in the child attributable to the father does match the set of

polymorphisms of the putative father, a statistical calculation can be performed to determine the probability of a coincidental match.

The probability of parentage exclusion (representing the probability that a random male will have a polymorphic form at a given polymorphic site that makes him incompatible as the father) is given by the equation (see WO 95/12607): p(exc) = xy(1-xy), where x and y are the population frequencies of alleles A and B of a biallelic polymorphic site.

(At a triallelic site p(exc) = xy(1-xy) + yz(1-yz) + xz(1-xz) + 3xyz(1-xyz)), where x, y, and z and the respective populations frequencies of alleles A, B, and C).

The probability of non-exclusion is: p(non-exc) = 1-p(exc).

The cumulative probability of non-exclusion (representing the values obtained when n loci are is used) is thus:

Cum p(non-exc) = p(non-exc1)p(non-exc2)p(non-exc3)...p(non-excn).

The cumulative probability of the exclusion for n loci (representing the probability that a random male will be excluded: cum p(exc) = 1 – cum p(non-exc).

If several polymorphic loci are included in the analysis, the cumulative probability of exclusion of a random male is very high. This probability can be taken into account in assessing the liability of a putative father whose polymorphic marker set matches the child's polymorphic marker set attributable to his or her father.

C. Kits

As set forth herein, the invention provides methods, *e.g.*, diagnostic and therapeutic methods, *e.g.*, for determining the type of allelic variant of a polymorphic region present in a PLCG1 or PAI-2 gene, such as a human PLCG1 or PAI-2 gene. In preferred embodiments, the methods use probes or primers comprising nucleotide sequences which are complementary polymorphic region of a PLCG1 or PAI-2 gene (SEQ ID NOs:5 and SEQ ID NO:6). Accordingly, the invention provides kits for performing these methods.

In a preferred embodiment, the invention provides a kit for determining whether a subject is or is not at risk of developing a disease or condition associated with a specific allelic variant of a PLCG1 or PAI-2 polymorphic region. In an even more preferred embodiment, the disease or disorder is characterized by an abnormal PLCG1 or PAI-2 activity. In an even more preferred embodiment, the invention provides a kit for determining whether a subject is or is not at risk of developing a vascular disease, *e.g.*, atherosclerosis, CAD, MI, ischemia, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism.

A preferred kit provides reagents for determining whether a subject is or is not likely to develop a vascular disease, *e.g.*, CAD or MI.

Preferred kits comprise at least one probe or primer which is capable of specifically hybridizing under stringent conditions to a PLCG1 or PAI-2 reference sequence or polymorphic region and instructions for use. The kits preferably comprise at least one of the above described nucleic acids. Preferred kits for amplifying at least a portion of a PLCG1 or PAI-2 gene, comprise at least two primer pairs, at least one of which is capable of hybridizing to an allelic variant sequence of a PLCG1 gene (*e.g.*, thymidine in the PLCG1 gene at residue 64001 of the reference sequence GI 11345540, or the complement thereof) and one of which is capable of hybridizing to a reference sequence of a PAI-2 gene (*e.g.*, thymidine at residue 170871 of the reference sequence GI 6705901, or the complement thereof).

The kits of the invention can also comprise one or more control nucleic acids or reference nucleic acids, such as nucleic acids comprising a PLCG1 or PAI-2 intronic sequence. For example, a kit can comprise primers for amplifying a polymorphic region of a PLCG1 or PAI-2 gene and a control DNA corresponding to such an amplified DNA and having the nucleotide sequence of a specific allelic variant. Thus, direct comparison can be performed between the DNA amplified from a subject and the DNA having the nucleotide sequence of a specific allelic variant. In one embodiment, the control nucleic acid comprises at least a portion of a PLCG1 or PAI-2 gene of an individual who does

not have a vascular disease, or a disease or disorder associated with an aberrant PLCG1 or PAI-2 activity.

Yet other kits of the invention comprise at least one reagent necessary to perform the assay. For example, the kit can comprise an enzyme. Alternatively the kit can comprise a buffer or any other necessary reagent.

D. Electronic Apparatus Readable Media and Arrays

Electronic apparatus readable media comprising polymorphisms of the present invention is also provided. As used herein, "electronic apparatus readable media" and "computer readable media," which are used interchangeably herein, refer to any suitable medium for storing, holding or containing data or information that can be read and accessed directly by an electronic apparatus. Such media can include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or configured for having recorded thereon a marker of the present invention.

As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet; electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can readily adopt any of the presently known methods for recording information on known media to generate manufactures comprising the polymorphisms of the present invention.

A variety of software programs and formats can be used to store the polymorphisms information of the present invention on the electronic apparatus readable medium. For example, the polymorphic sequence can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like, as well as in other forms. Any number of data processor structuring formats (*e.g.*, text file or database) may be employed in order to obtain or create a medium having recorded thereon the markers of the present invention.

By providing the polymorphisms of the invention in readable form, singly or in combination, one can routinely access the polymorphism information for a variety of purposes. For example, one skilled in the art can use the sequences of the polymorphisms of the present invention in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences of the invention which match a particular target sequence or target motif.

The present invention therefore provides a medium for holding instructions for performing a method for determining whether a subject has a vascular disease or a pre-disposition to a vascular disease, wherein the method comprises the steps of determining the presence or absence of a polymorphism and based on the presence or absence of the polymorphism, determining whether the subject has a vascular disease or a pre-disposition to a vascular disease and/or recommending a particular clinical course of therapy or diagnostic evaluation for the vascular disease or pre-vascular disease condition.

The present invention further provides in an electronic system and/or in a network, a method for determining whether a subject has a vascular disease or a pre-disposition to vascular disease associated with a polymorphism as described herein wherein the method comprises the steps of determining the presence or absence of the polymorphism, and based on the presence or absence of the polymorphism, determining

whether the subject has a vascular disease or a pre-disposition to a vascular disease, and/or recommending a particular treatment for the vascular disease or pre-vascular disease condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject .

The present invention also provides in a network, a method for determining whether a subject has vascular disease or a pre-disposition to vascular disease associated with a polymorphism, said method comprising the steps of receiving information associated with the polymorphism, receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the polymorphism and/or vascular disease, and based on one or more of the phenotypic information, the polymorphism, and the acquired information, determining whether the subject has a vascular disease or a pre-disposition to a vascular disease. The method may further comprise the step of recommending a particular treatment for the vascular disease or pre-vascular disease condition.

The present invention also provides a method for determining whether a subject has a vascular disease or a pre-disposition to a vascular disease, said method comprising the steps of receiving information associated with the polymorphism, receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the polymorphism and/or vascular disease, and based on one or more of the phenotypic information, the polymorphism, and the acquired information, determining whether the subject has vascular disease or a pre-disposition to vascular disease. The method may further comprise the step of recommending a particular treatment for the vascular disease or pre-vascular disease condition.

E. Personalized Health Assessment

Methods and systems of assessing personal health and risk for disease, *e.g.*, vascular disease, in a subject, using the polymorphisms and association of the instant invention are also provided. The methods provide personalized health care knowledge to

individuals as well as to their health care providers, as well as to health care companies. It will be appreciated that the term "health care providers" is not limited to physicians but can be any source of health care. The methods and systems provide personalized information including a personal health assessment report that can include a personalized molecular profile, *e.g.*, an PLCG1 and/or PAI-2 genetic profile, a health profile, or both. Overall, the methods and systems as described herein provide personalized information for individuals and patient management tools for healthcare providers and/or subjects using a variety of communications networks such as, for example, the Internet. U.S. Patent Application Serial No. 60/266,082, filed February 1, 2001, entitled "Methods and Systems for Personalized Health Assessment," further describes personalized health assessment methods, systems, and apparatus, and is expressly incorporated herein by reference.

In one aspect, the invention provides an Internet-based method for assessing a subject's risk for vascular disease, *e.g.*, CAD or MI. In one embodiment, the method comprises obtaining a biological sample from a subject, analyzing the biological sample to determine the presence or absence of a polymorphic region of PLCG1 and/or PAI-2, and providing results of the analysis to the subject via the Internet, wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease. In another embodiment, the method comprises analyzing data from a biological sample from a subject relating to the presence or absence of a polymorphic region of PLCG1 and/or PAI-2 and providing results of the analysis to the subject via the Internet, wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a or decreased risk for vascular disease.

It will be appreciated that the phrase "wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease" includes a decreased or lower than normal risk of developing a vascular disease indicated the presence of two copies of a thymidine allele at nucleotide position 170871 of the PAI-2 gene together with two copies of a thymidine allele at nucleotide position 64001 of the PLCG1 gene, or the complements thereof, or the presence of a threonine at amino acid

position 813 of the PLCG1 protein and the presence an asparagine at amino acid position 120 of the PAI-2 protein.

The terms "Internet" and/or "communications network" as used herein refer to any suitable communication link, which permits electronic communications. It should be understood that these terms are not limited to "the Internet" or any other particular system or type of communication link. That is, the terms "Internet" and/or "communications network" refer to any suitable communication system, including extra-computer system and intra-computer system communications. Examples of such communication systems include internal busses, local area networks, wide area networks, point-to-point shared and dedicated communications, infra-red links, microwave links, telephone links, CATV links, satellite and radio links, and fiber-optic links. The terms "Internet" and/or "communications network" can also refer to any suitable communications system for sending messages between remote locations, directly or via a third party communication provider such as AT&T. In this instance, messages can be communicated via telephone or facsimile or computer synthesized voice telephone messages with or without voice or tone recognition, or any other suitable communications technique.

In another aspect, the methods of the invention also provide methods of assessing a subject's risk for vascular disease, *e.g.*, CAD or MI. In one embodiment, the method comprises obtaining information from the subject regarding the polymorphic region of an PLCG1 and/or PAI-2 gene, through *e.g.*, obtaining a biological sample from the individual, analyzing the sample to obtain the subject's PLCG1 and/or PAI-2 genetic profile, representing the PLCG1 and/or PAI-2 genetic profile information as digital genetic profile data, electronically processing the PLCG1 and/or PAI-2 digital genetic profile data to generate a risk assessment report for vascular disease, and displaying the risk assessment report on an output device, where the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease. In another embodiment, the method comprises analyzing a subject's PLCG1 and/or PAI-2 genetic profile, representing the PLCG1 and/or PAI-2 genetic profile information as digital

genetic profile data, electronically processing the PLCG1 and/or PAI-2 digital genetic profile data to generate a risk assessment report for vascular disease, and displaying the risk assessment report on an output device, where the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease, *e.g.*, CAD or MI. Additional health information may be provided and can be utilized to generate the risk assessment report. Such information includes, but is not limited to, information regarding one or more of age, sex, ethnic origin, diet, sibling health, parental health, clinical symptoms, personal health history, blood test data, weight, and alcohol use, drug use, nicotine use, and blood pressure.

The PLCG1 and/or PAI-2 digital genetic profile data may be transmitted via a communications network, *e.g.*, the Internet, to a medical information system for processing.

In yet another aspect the invention provides a medical information system for assessing a subject's risk for vascular disease comprising a means for obtaining information from the subject regarding the polymorphic region of an PLCG1 and/or PAI-2 gene, through *e.g.*, obtaining a biological sample from the individual to obtain an PLCG1 and/or PAI-2 genetic profile, a means for representing the PLCG1 and/or PAI-2 genetic profile as digital molecular data, a means for electronically processing the PLCG1 and/or PAI-2 digital genetic profile to generate a risk assessment report for vascular disease, and a means for displaying the risk assessment report on an output device, where the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease.

In another aspect, the invention provides a computerized method of providing medical advice to a subject comprising obtaining information from the subject regarding the polymorphic region of an PLCG1 and/or PAI-2 gene, through *e.g.*, obtaining a biological sample from the subject, analyzing the subject's biological sample to determine the subject's PLCG1 and/or PAI-2 genetic profile, and, based on the subject's PLCG1 and/or PAI-2 genetic profile, determining the subject's risk for vascular disease. Medical advice may be then provided electronically to the subject, based on the

subject's risk for vascular disease. The medical advice may comprise, for example, recommending one or more of the group consisting of: further diagnostic evaluation, use of medical or surgical devices, administration of medication, or lifestyle change. Additional health information may also be obtained from the subject and may also be used to provide the medical advice.

In another aspect, the invention includes a method for self-assessing risk for a vascular disease. The method comprises providing information from the subject regarding the polymorphic region of an PLCG1 and/or PAI-2 gene, through *e.g.*, providing a biological sample for genetic analysis, and accessing an electronic output device displaying results of the genetic analysis, thereby self-assessing risk for a vascular disease, where the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease.

In another aspect, the invention provides a method of self-assessing risk for vascular disease comprising providing information from the subject regarding the polymorphic region of an PLCG1 and/or PAI-2 gene, through *e.g.*, providing a biological sample, accessing PLCG1 and/or PAI-2 digital genetic profile data obtained from the biological sample, the PLCG1 and/or PAI-2 digital genetic profile data being displayed via an output device, where the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease.

An output device may be, for example, a CRT, printer, or website. An electronic output device may be accessed via the Internet.

The biological sample may be obtained from the individual at a laboratory company. In one embodiment, the laboratory company processes the biological sample to obtain PLCG1 and/or PAI-2 genetic profile data, represents at least some of the PLCG1 and/or PAI-2 genetic profile data as digital genetic profile data, and transmits the PLCG1 and/or PAI-2 digital genetic profile data via a communications network to a medical information system for processing. The biological sample may also be obtained from the subject at a draw station. A draw station processes the biological sample to obtain PLCG1 and/or PAI-2 genetic profile data and transfers the data to a laboratory

company. The laboratory company then represents at least some of the PLCG1 and/or PAI-2 genetic profile data as digital genetic profile data, and transmits the PLCG1 and/or PAI-2 digital genetic profile data via a communications network to a medical information system for processing.

In another aspect, the invention provides a method for a health care provider to generate a personal health assessment report for an individual. The method comprises counseling the individual to provide a biological sample and authorizing a draw station to take a biological sample from the individual and transmit molecular information from the sample to a laboratory company, where the molecular information comprises the presence or absence of a polymorphic region of PLCG1 and/or PAI-2. The health care provider then requests the laboratory company to provide digital molecular data corresponding to the molecular information to a medical information system to electronically process the digital molecular data and digital health data obtained from the individual to generate a health assessment report, receives the health assessment report from the medical information system, and provides the health assessment report to the individual.

In still another aspect, the invention provides a method of assessing the health of an individual. The method comprises obtaining health information from the individual using an input device (*e.g.,* a keyboard, touch screen, hand-held device, telephone, wireless input device, or interactive page on a website), representing at least some of the health information as digital health data, obtaining a biological sample from the individual, and processing the biological sample to obtain molecular information, where the molecular information comprises the presence or absence of a polymorphic region of PLCG1 and/or PAI-2. At least some of the molecular information and health data is then presented as digital molecular data and electronically processed to generate a health assessment report. The health assessment report is then displayed on an output device. The health assessment report can comprise a digital health profile of the individual. The molecular data can comprise protein sequence data, and the molecular profile can comprise a proteomic profile. The molecular data can also comprise information

regarding one or more of the absence, presence, or level, of one or more specific proteins, polypeptides, chemicals, cells, organisms, or compounds in the individual's biological sample. The molecular data may also comprise, *e.g.*, nucleic acid sequence data, and the molecular profile may comprise, *e.g.*, a genetic profile.

In yet another embodiment, the method of assessing the health of an individual further comprises obtaining a second biological sample or a second health information at a time after obtaining the initial biological sample or initial health information, processing the second biological sample to obtain second molecular information, processing the second health information, representing at least some of the second molecular information as digital second molecular data and second health information as digital health information, and processing the molecular data and second molecular data and health information and second health information to generate a health assessment report. In one embodiment, the health assessment report provides information about the individual's predisposition for vascular disease, *e.g.*, CAD or MI, and options for risk reduction.

Options for risk reduction comprise, for example, one or more of diet, exercise, one or more vitamins, one or more drugs, cessation of nicotine use, and cessation of alcohol use. wherein the health assessment report provides information about treatment options for a particular disorder. Treatment options comprise, for example, one or more of diet, one or more drugs, physical therapy, and surgery. In one embodiment, the health assessment report provides information about the efficacy of a particular treatment regimen and options for therapy adjustment.

In another embodiment, electronically processing the digital molecular data and digital health data to generate a health assessment report comprises using the digital molecular data and/or digital health data as inputs for an algorithm or a rule-based system that determines whether the individual is at risk for a specific disorder, *e.g.*, a vascular disorder, such as CAD or MI. Electronically processing the digital molecular data and digital health data may also comprise using the digital molecular data and digital health data as inputs for an algorithm or a rule-based system based on one or more

databases comprising stored digital molecular data and/or digital health data relating to one or more disorders, *e.g.*, vascular disorders, such as CAD or MI.

In another embodiment, processing the digital molecular data and digital health data comprises using the digital molecular data and digital health data as inputs for an algorithm or a rule-based system based on one or more databases comprising: (i) stored digital molecular data and/or digital health data from a plurality of healthy individuals, and (ii) stored digital molecular data and/or digital health data from one or more pluralities of unhealthy individuals, each plurality of individuals having a specific disorder. At least one of the databases can be a public database. In one embodiment, the digital health data and digital molecular data are transmitted via, *e.g.*, a communications network, *e.g.*, the Internet, to a medical information system for processing.

A database of stored molecular data and health data, *e.g.*, stored digital molecular data and/or digital health data, from a plurality of individuals, is further provided. A database of stored digital molecular data and/or digital health data from a plurality of healthy individuals, and stored digital molecular data and/or digital health data from one or more pluralities of unhealthy individuals, each plurality of individuals having a specific disorder, *e.g.*, a vascular disorder, is also provided.

The new methods and systems of the invention provide healthcare providers with access to ever-growing relational databases that include both molecular data and health data that is linked to specific disorders, *e.g.*, vascular disorders. In addition public medical knowledge is screened and abstracted to provide concise, accurate information that is added to the database on an ongoing basis. In addition, new relationships between particular SNPs, *e.g.*, SNPs associated with vascular disease, or genetic mutations and specific discords are added as they are discovered.

The present invention is further illustrated by the following examples which should not be construed as limiting in any way. The contents of all cited references (including, without limitation, literature references, issued patents, published patent applications and database records including Genbank™ records) as cited throughout this application are hereby expressly incorporated by reference. The practice of the present

invention will employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, *Molecular Cloning A Laboratory Manual*, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press: 1989); *DNA Cloning*, Volumes I and II (D. N. Glover ed., 1985); *Oligonucleotide Synthesis* (M. J. Gait ed., 1984); Mullis *et al.* U.S. Patent No: 4,683,195; *Nucleic Acid Hybridization* (B. D. Hames & S. J. Higgins eds. 1984); *Transcription And Translation* (B. D. Hames & S. J. Higgins eds. 1984); *Culture Of Animal Cells* (R. I. Freshney, Alan R. Liss, Inc., 1987); *Immobilized Cells And Enzymes* (IRL Press, 1986); B. Perbal, *A Practical Guide To Molecular Cloning* (1984); the treatise, *Methods In Enzymology* (Academic Press, Inc., N.Y.); *Gene Transfer Vectors For Mammalian Cells* (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); *Methods In Enzymology*, Vols. 154 and 155 (Wu *et al.* eds.), *Immunochemical Methods In Cell And Molecular Biology* (Mayer and Walker, eds., Academic Press, London, 1987); *Handbook Of Experimental Immunology*, Volumes I-IV (D. M. Weir and C. C. Blackwell, eds., 1986); *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986).

EXAMPLES

Example 1: Detection of polymorphic regions in the human PLCG1 and PAI-2 genes

This example describes the detection of polymorphic regions in the human PLCG1 and PAI-2 genes through use of denaturing high performance liquid chromatography (DHPLC), variant detector arrays, polymerase chain reaction (PCR), and direct sequencing.

Cell lines derived from an ethnically diverse population were obtained and used for single nucleotide polymorphism (SNP) discovery by methods described in Cargill, *et al.* (1999) *Nature Genetics* 22:231-238, incorporated herein in its entirety by reference.

Genomic sequence representing the coding and partial regulatory regions of genes were amplified by polymerase chain reaction and screened via two independent methods: denaturing high performance liquid chromatography (DHPLC) or variant detector arrays (Affymetrix™).

DHPLC uses reverse-phase ion-pairing chromatography to detect the heteroduplexes that are generated during amplification of PCR fragments from individuals who are heterozygous at a particular nucleotide locus within that fragment (Oefner and Underhill (1995) *Am. J. Human Gen.* 57:Suppl. A266).

Generally, the analysis was carried out as described in O'Donovan *et al.* ((1998) Genomics 52:44-49). PCR products having product sizes ranging from about 150-400 bp were generated. Two PCR reactions were pooled together for DHPLC analysis (4 ul of each reaction for a total of 8 ul per sample). DHPLC was performed on a DHPLC system purchased from Transgenomic, Inc. The gradient was created by mixing buffers A (0.1M TEAA) and B (0.1M TEAA, 25% Acetontitrile). WAVEmaker™ software was utilized to predict a melting temperature and calculate a buffer gradient for mutation analysis of a given DNA sequence. The resulting chromatograms were analyzed to identify base pair alterations or deletions based on specific chromatographic profiles.

Detection of polymorphic regions in the human PLCG1 and PAI-2 genes by SSCP

Genomic DNA from the cell lines derived from an ethnically diverse population as described in Cargill, *et al.* (1999) *Nature Genetics* 22:231-238, was subjected to PCR in 25 µl reactions (1X PCR Amplitaq polymerase buffer, 0.1 mM dNTPs, 0.8 µM 5' primer, 0.8 µM 3' primer, 0.75 units of Amplitaq polymerase, 50 ng genomic DNA) using each of the above described pairs of primers under the following cycle conditions: 94°C for 2 min, 35 x [94°C for 40 sec, 57°C for 30 sec, 72°C for 1 min], 72°C 5 min, 4°C hold.

The amplified genomic DNA fragments were then analyzed by SSCP (Orita *et al.* (1989) *PNAS USA* 86:2766, see also Cotton (1993) *Mutat Res* 285:125-144; and Hayashi (1992) *Genet Anal Tech Appl* 9:73-79). From each 25 µl PCR reaction, 3 µl was taken

and added to 7 µl of loading buffer. The mixture was heated to 94°C for 5 min and then immediately cooled in a slurry of ice-water. 3-4 µl were then loaded on a 10% polyacrylamide gel either with 10% glycerol or without 10% glycerol, and then subjected to electrophoresis either overnight at 4 Watts at room temperature, overnight at 4 Watts at 4°C (for amplifying a 5' upstream regulatory element), or for 5 hours at 20 Watts at 4°C. The secondary structure of single-stranded nucleic acids varies according to sequence, thus allowing the detection of small differences in nucleic acid sequence between similar nucleic acids. At the end of the electrophoretic period, the DNA was analyzed by gently overlaying a mixture of dyes onto the gel (1x the manufacturer's recommended concentration of SYBR Green I™ and SYBR Green II™ in 0.5 X TBE buffer (Molecular Probes™)) for 5 min, followed by rinsing in distilled water and detection in a Fluoroimager 575™ (Molecular Dynamics™).

Sequencing of PCR products

To determine the sequences of the polymorphisms identified, the regions containing the polymorphisms were reamplified using flanking primers. The genomic DNA was subjected to PCR in 50 µl reactions (1x PCR Amplitaq polymerase buffer, 0.1 mM dNTPs, 0.8 µM 5' primer, 0.8 µM 3' primer, 0.75 units of Amplitaq polymerase, 50 ng genomic DNA) using each of the pairs of primers under the following cycle conditions: 94°C for 2 min, 35 x [94°C for 40 sec, 57°C for 30 sec, 72°C for 1 min], 72°C 5 min, 4°C hold. The newly amplified products were then purified using the Qiagen Qiaquick PCR purification kit according to the manufacturer's protocol, and subjected to sequencing using the aforementioned primers which were utilized for amplification.

Results

Several SNPs in each of the PLCG1 and PAI2 genes were identified. Two SNPs in the PLCG1 gene and four SNPs in the PAI2 gene were selected for further analysis. The two SNPs in the PLCG1 gene were in strong linkage disequilibrium with each other

($p<.0001$). The four SNPs in the PAI-2 gene were in strong linkage disequilibrium with each other (all pairwise p values <.0001). Table 1 lists all of the SNPs analyzed in the PLCG1 gene and PAI-2 gene. Table 2 shows the measure of linkage disequilibrium between pairs of SNPs in each gene.

Further analysis of the PLCG1 and PAI-2 SNPs included genotyping of the SNPs in large patient populations to assess their association with CAD and MI. A total of 352 U.S. Caucasian subjects with premature coronary artery disease were identified in 15 participating medical centers, fulfilling the criteria of either myocardial infarction, surgical or percutaneous revascularization, or a significant coronary artery lesion (*e.g.*, at least a 70% stenosis in a major epicardial artery) diagnosed before age 45 in men or age 50 in women and having a living sibling who met the same criteria. The sibling with the earliest onset in a Caucasian subset of these families was compared with a random sample of 418 Caucasian controls without known coronary disease. Controls representing a general, unselected population were identified through random-digit dialing in the Atlanta, Georgia area. Subjects ranging in age from age 20 to age 70 were invited to participate in the study. The subjects answered a health questionnaire, had anthropometric measures taken, and blood drawn for measurement of serum markers and extraction of DNA. Demographic characteristics are shown in Figure 5.

Table 1.

Gene	SNP	nt. change	Amino acid change	Flanking sequence	GI number/ nucleotide (nt) position	SEQ ID NO:
PLCG1	G329u1	c/t	I/T	ACGAGCTGA CCTTCAcCAA GAGCGCCAT CAT	GI 11345540 nt 64001	5
PLCG1	G329u3	a/g	S/G	CAGGAGTTC ATGCTCgGCT TCCTCCGAG ACC	GI 11345540 nt 58599	7
PAI-2	PAI2u1	t/c	N/D	AAATAATcC CCTGTGGA	GI 6705901 nt 170871	6
PAI-2	PAI2u5	c/g	S/C	TTTTCGGCA GATTTTgCTC ACCCTAAAA CTA	GI 6705901 nt 164736	8
PAI-2	PAI2u4	c/g	N/K	GCATAAGAT AACCAAgTG CATTTTATTT TTC	GI 6705901 nt 164762	9
PAI-2	PAI2d17	c/g	non-coding	TGTTTTTTTC TTCCTgTCTT TGCTTCTAG AT	GI 6705901 nt 176579	10

Table 2.

Gene	**SNP1**	**SNP2**	**D'**	**P value**
PLCG1	G329u1	G329u3	.96	<.0001
PAI2	PAI2u5	PAI2u4	1.00	<.0001
PAI2	PAI2u5	PAI2u1	.99	<.0001
PAI2	PAI2u5	PAI2d17	.80	<.0001
PAI2	PAI2u4	PAI2u1	.99	<.0001
PAI2	PAI2u4	PAI2d17	.80	<.0001
PAI2	PAI2u1	PAI2d17	.77	<.0001

One SNP from each of the PLCG1 and PAI-2 genes showed strong associations with CAD and/or MI. These SNPs were a change from a cytidine (C) to a thymidine (T) in the PLCG1 gene at residue 64001 of the reference sequence GI 11345540 (polymorphism ID No. G329u1) and a change from a thymidine (T) to a cytidine (C) in the PAI-2 gene at residue 170871 of the reference sequence GI 6705901 (polymorphism

ID No. PAI2u1) (see Table 3, below). Because other SNPs in PLCG1 and PAI2 have been demonstrated to be in strong linkage disequilibrium with these specific SNPs, G329u1 and PAI2u1, these other SNPs could be used as surrogates, *e.g.*, markers, of G329u1 and PAI2u1 to predict risk of CAD and/or MI in a subject.

Table 3.

1	2	3	4	5	6	7	8	9	10
Gene	**PolyID**	**var freq**	**Type of variant**	**Geno-types**	**Ref**	**Var**	**Genbank Accession/nt position**	**Flanking sequence**	**SEQ ID NO.**
PLCG1	G329u1	.25	Missense (I/T)	TT TC CC	C	T	GI:11345540/nt 64001	GACCTTCA tCAAGAGC G	5
PAI2	PAI2u1	.22	Missense (N/D)	CC CT TT	T	C	GI:6705901/nt 170871	AAATAATc CCCTGTG GA	6

Example 2: Statistical Analysis

All analyses were done using the SAS statistical package (Version 8.0, SAS Institute Inc., Cary, N.C.). Differences between cases and controls were assessed with a chi-square statistic for categorical covariates and the Wilcoxon statistic for continuous covariates. Association between each SNP and two outcomes, CAD and MI, was measured by comparing genotype frequencies between controls and all CAD cases and the subset of cases with MI. Significance was determined using a continuity-adjusted chi-square or Fisher's exact test for each genotype compared to the homozygotes wild-type for that locus. Odds ratios were calculated and presented with 95% confidence intervals.

Genotype groups were pooled for subsequence analysis of the top loci. Pooling allows the best model for each locus (dominant, codominant, or recessive) to be tested. Models were chosen based on significant differences between genotypes within a locus. A recessive model was chosen when the homozygous variant differed significantly from

both the heterozygous and homozygous wildtype, and the latter two did not differ from each other. A codominant model was chosen when homozygous variant genotypes differed from both heterozygous and homozygous wild-type, and the latter two differed significantly from each other. A dominant model was chosen when no significant difference was observed between heterozygous and homozygous variant genotypes.

Multivariate logistic regression was used to adjust for sex, presence of hypertension, diabetes, and body mass index using the LOGISTC procedure in SAS. Height and weight, measured at the time of enrollment, were used to calculate body mass index for each subject. Presence of hypertension and non-insulin-dependent diabetes was measures by self-report (controls) and medical record confirmation (cases).

Two SNPs, one from the PLCG1 gene and one from the PAI-2 gene showed statistically significant differences from cases and controls for CAD and/or MI (defined as $p<.05$). CAD and MI odds ratios for these polymorphisms are shown in Table 4, below. Individuals who are homozygous for the variant of the PLGC1 SNP G329u1 (*i.e.*, TT), or the complement thereof, are approximately 1.5-fold less likely to develop CAD and/or MI than individuals without this genotype. Individuals who are homozygous for the reference allele of the PAI-2 SNP PAIu1 (*i.e.*, TT), or the complement thereof, are approximately 1.5-fold less likely to develop CAD and/or MI than individuals without this genotype. Individuals who are both homozygous for the variant of the PLGC1 SNP G329u1 (*i.e.*, TT genotype) and homozygous for the reference allele of the PAI-2 SNP PAIu1 (*i.e.*, TT), or the complements thereof, are approximately 3-fold less likely to develop CAD and/or MI than individuals with any other combination (odds ratio CAD: 0.39 (.22, .68); odds ratio MI: 0.32 (.15, .70)).

Table 4.

Gene	PolyID	Geno-type	Controls	CAD cases	MI cases	CAD Odds Ratio (95% confidence interval)	MI Odds Ratio (95% confidence interval)
PLCG1	G329u1	TT	87	50	29	0.66 (.44, .98) *	.72 (.44, 1.12)
		TC/CC	326	284	151	1.00	1.00
PAI-2	PAI2u1	AA	235	163	80	0.75 (.55, 1.02)	0.62 (.42, .91)*
		GA/GG	153	142	84	1.00	1.00
both PLCG1 and PAI-2	G329u1 and PAIu1	TT (G329u1) and AA (PAI2u1) vs all other	56	18	8	0.39 (.22, .68)*	0.32 (.15, .69)*
			328	272	146	1.00	1.00

* $p<.05$

Possible combinations of these alleles are listed in Table 5, below. As discussed above, individuals who are homozygous for the variant of the PLGC1 SNP G329u1 (TT) and homozygous for the reference allele of the PAI-2 SNP PAIu1 (TT), or the complements thereof, are approximately 3-fold less likely to develop a vascular disease or disorder compared to individuals with any other possible combination.

Table 5.

Gene (polyID)	PLCG1 (G329u1)	PAI-2 (PAIu1)
	TT	CC
	TT	TC
**	TT	TT
	TC	CC
	TC	TC
	TC	TT
	CC	CC
	CC	TC
	CC	TT

**3-fold less likely to develop CAD and/or MI compared to all other possible combinations

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A method for diagnosing or aiding in the diagnosis of a vascular disease or disorder in a subject comprising the steps of determining the PLCG1 and PAI-2 genetic profile of the subject, thereby diagnosing or aiding in the diagnosis of a vascular disease or disorder.

2. The method of claim 1, wherein determining the subject's PLCG1 and PAI-2 genetic profile comprises determining the identity of the nucleotide present at nucleotide position 64001 of SEQ ID NO:1 and the nucleotide present at nucleotide position 170871 of SEQ ID NO:3, or the complement thereof.

3. The method of claim 1, wherein determining the subject's PLCG1 and PAI-2 genetic profile comprises determining the identity of the amino acid present at amino acid residue 813 of SEQ ID NO:2 and the amino acid present at amino acid residue 120 of SEQ ID NO:4, or the complement thereof.

4. The method of claim 1, wherein the vascular disease is myocardial infarction.

5. The method of claim 1, wherein the vascular disease is coronary artery disease.

6. A method for predicting the likelihood that a subject will or will not develop a vascular disease or disorder comprising the steps of determining the PLCG1 and PAI-2 genetic profile of the subject, thereby predicting the likelihood that a subject will or will not develop a vascular disease or disorder.

7. The method of claim 6, wherein determining the subject's PLCG1 and PAI-2 genetic profile comprises determining the identity of the nucleotide present at nucleotide position 64001 of SEQ ID NO:1 and the nucleotide present at nucleotide position 170871 of SEQ ID NO:3, or the complement thereof.

8. The method of claim 6, wherein determining the subject's PLCG1 and PAI-2 genetic profile comprises determining the identity of the amino acid present at amino acid residue 813 of SEQ ID NO:2 and/or the amino acid present at amino acid residue 120 of SEQ ID NO:4, or the complement thereof.

9. The method of claim 6, wherein the vascular disease is myocardial infarction.

10. The method of claim 6, wherein the vascular disease is coronary artery disease.

11. A method of diagnosing or aiding in the diagnosis of a vascular disease in a subject comprising the steps of determining the nucleotide present at nucleotide position 170871 of the PAI-2 gene and determining the nucleotide present at nucleotide position 64001 of the PLCG1 gene, wherein the presence of two copies of a thymidine allele at nucleotide position 170871 of the PAI-2 gene together with two copies of a thymidine allele at nucleotide position 64001 of the PLCG1 gene, or the complements thereof, is indicative of decreased likelihood of a vascular disease in the subject as compared with a subject having any other combination of these alleles.

12. The method of claim 11, wherein determining said nucleotides comprises obtaining a nucleic acid sample from the subject.

13. The method of claim 11, wherein the PLCG1 gene has the nucleotide sequence of SEQ ID NO:1, or a portion thereof, and wherein the PAI-2 gene has the nucleotide sequence of SEQ ID NO:3, or a portion thereof.

14. The method of claim 11, wherein the vascular disease is selected from the group consisting of atherosclerosis, coronary artery disease, myocardial infarction, ischemia, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism.

15. The method of claim 14, wherein the vascular disease is myocardial infarction.

16. The method of claim 14, wherein the vascular disease is coronary artery disease.

17. A method for predicting the likelihood that a subject will or will not develop a vascular disease, comprising the steps of determining the nucleotide present at nucleotide position 170871 of the PAI-2 gene and determining the nucleotide present at nucleotide position 64001 of the PLCG1 gene, wherein the presence of two thymidine alleles at nucleotide position 170871 of the PAI-2 gene and the presence of two thymidine alleles at nucleotide position 64001 of the PLCG1 gene, or the complements thereof, is indicative of decreased likelihood of the subject developing a vascular disease as compared with a subject having any other combination of these alleles.

18. The method of claim 17, wherein determining said nucleotides comprises obtaining a nucleic acid sample from the subject.

19. The method of claim 17, wherein the PLCG1 gene has the nucleotide sequence of SEQ ID NO:1, or a portion thereof, and wherein the PAI-2 gene has the nucleotide sequence of SEQ ID NO:3, or a portion thereof.

20. The method of claim 17, wherein the vascular disease is selected from the group consisting of atherosclerosis, coronary artery disease, myocardial infarction, ischemia, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism.

21. The method of claim 20, wherein the vascular disease is myocardial infarction.

22. The method of claim 21, wherein the vascular disease is coronary artery disease.

23. A method of diagnosing or aiding in the diagnosis of a vascular disease in a subject comprising the steps of determining the amino acid present at amino acid position 120 of the PAI-2 protein and determining the amino acid present at amino acid position 813 of the PLCG1 protein, wherein presence of a threonine at amino acid position 813 of the PLCG1 protein and the presence of an asparagine at amino acid position 120 of the PAI-2 protein is indicative of decreased likelihood of a vascular disease in the subject as compared with a subject having any other combination of these amino acids.

24. The method of claim 23, wherein determining said amino acids comprises obtaining a protein sample from the subject.

25. The method of claim 23, wherein the PLCG1 protein has the amino acid sequence of SEQ ID NO:2, or a portion thereof and wherein the PAI-2 protein has the amino acid sequence of SEQ ID NO:4, or a portion thereof.

26. The method of claim 23, wherein the vascular disease is selected from the group consisting of atherosclerosis, coronary artery disease, myocardial infarction, ischemia, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism.

27. The method of claim 25, wherein the vascular disease is myocardial infarction.

28. The method of claim 25, wherein the vascular disease is coronary artery disease.

29. A method for predicting the likelihood that a subject will not develop a vascular disease, comprising the steps of determining the amino acid present at amino acid position 120 of the PAI-2 protein and determining the amino acid present at amino acid position 813 of the PLCG1 protein, wherein presence of a threonine at amino acid position 813 of the PLCG1 protein and the presence of an asparagine at amino acid position 120 of the PAI-2 protein is indicative of decreased likelihood of a subject developing a vascular disease as compared with a subject having any other combination of these amino acids.

30. The method of claim 29, wherein determining said amino acids comprises obtaining a protein sample from the subject.

31. The method of claim 29, wherein the PLCG1 protein has the amino acid sequence of SEQ ID NO:2, or a portion thereof and wherein the PAI-2 protein has the amino acid sequence of SEQ ID NO:4, or a portion thereof.

32. The method of claim 29, wherein the vascular disease is selected from the group consisting of atherosclerosis, coronary artery disease, myocardial infarction, ischemia, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism.

33. The method of claim 29, wherein the vascular disease is myocardial infarction.

34. The method of claim 32, wherein the vascular disease is coronary artery disease.

35. A computer readable medium for storing instructions for performing a computer implemented method for determining whether or not a subject has a predisposition to a vascular disease or disorder, said instructions comprising the functionality of:

obtaining information from the subject indicative of the presence or absence of the polymorphic region of a PLCG1 and/or PAI-2 gene, and

based on the presence or absence of the polymorphic region of a PLCG1 and/or PAI-2 gene, determining whether or not the subject has a predisposition to a vascular disease or disorder.

36. A computer readable medium for storing instructions for performing a computer implemented method for identifying a predisposition to a vascular disease or disorder, said instructions comprising the functionality of:

obtaining information regarding the presence or absence of the polymorphic region of a PLCG1 and/or PAI-2 gene, and

based on the presence or absence of the polymorphic region of a PLCG1 and/or PAI-2 gene, identifying a predisposition to a vascular disease or disorder.

37. An electronic system comprising a processor for determining whether or not a subject has a predisposition to a vascular disease or disorder, said processor implementing the functionality of:

obtaining information from the subject indicative of the presence or absence of the polymorphic region of a PLCG1 and/or PAI-2 gene, and

based on the presence or absence of the polymorphic region of a PLCG1 and/or PAI-2 gene, determining whether or not the subject has the predisposition to a vascular disease or disorder.

38. An electronic system comprising a processor for performing a method for identifying a predisposition to a vascular disease or disorder in a subject, said processor implementing the functionality of:

obtaining information from the subject indicative of the presence or absence of the polymorphic region of a PLCG1 and/or PAI-2 gene, and

based on the presence or absence of the polymorphic region of a PLCG1 and/or PAI-2 gene, performing a method for identifying a predisposition to a vascular disease or disorder associated with the polymorphic region.

39. The electronic system of claims 37 or 38, wherein said processor further implements the functionality of receiving phenotypic information associated with the subject.

40. The electronic system of claims 37 or 38, wherein said processor further implements the functionality of acquiring from a network phenotypic information associated with the subject.

41. A network system for identifying a predisposition to a vascular disease or disorder in response to information submitted by an individual, said system comprising means for:

receiving data from the individual regarding the presence or absence of the polymorphic region of a PLCG1 and/or PAI-2 gene, and

based on the presence or absence of the polymorphic region, determining whether or not the subject has the predisposition to the vascular disease or disorder associated with the polymorphic region.

42. A network system for identifying whether or not a subject has a predisposition to a vascular disease or disorder, said system comprising means for:

receiving information from the subject regarding the polymorphic region of a PLCG1 and/or PAI-2 gene,

receiving phenotypic information associated with the subject,

acquiring additional information from the network, and

based on one or more of the phenotypic information, the polymorphic region, and the acquired information, determining whether or not the subject has a pre-disposition to a vascular disease or disorder associated with a polymorphic region of a PLCG1 and/or PAI-2 gene.

43. The system of claims 41 and 42, wherein the network system comprises a server and a work station operatively connected to said server via the network.

44. A composition comprising an isolated nucleic acid molecule comprising an allelic variant of a polymorphic region of a PLCG1 gene, wherein the allelic variant

differs from the reference sequence set forth in SEQ ID NO:1, or a portion thereof, and wherein the allelic variant is associated with aberrant PLCG1 activity, in combination with an isolated nucleic acid molecule comprising an allelic variant of a polymorphic region of a PAI-2 gene, wherein the allelic variant does not differ from the reference sequence set forth in SEQ ID NO:3, or a portion thereof, and wherein the allelic variant is associated with aberrant PAI-2 activity.

45. The composition of claim 44, wherein the polymorphic regions are located in an exon.

46. A composition comprising an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, or a portion thereof, further comprising the nucleotide sequence of SEQ ID NO:5, or the complement thereof, in combination with an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:3, or a portion thereof, further comprising the nucleotide sequences of SEQ ID NO:6, or the complement thereof.

47. A composition comprising an isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:1, or a portion thereof, wherein residue 64001 is a thymidine, or the complement thereof, in combination with an isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:3, or a portion thereof, wherein residue 170871 is a thymidine, or the complement thereof.

48. A kit comprising probes or primers which are capable of hybridizing to the nucleic acid molecules of any of claims 44-47.

49. The kit of claim 48, wherein the probes or primers comprise a nucleotide sequence from about 15 to about 30 nucleotides.

50. The kit of claim 48, wherein the probes or primers are labeled.

51. A method for determining the identity of one or more allelic variants of a polymorphic region of a PLCG1 gene and a PAI-2 gene in a nucleic acid obtained from a subject, comprising contacting a sample nucleic acid from the subject with a probe or primer having a sequence which is complementary to a PLCG1 gene sequence and a probe or primer which is complementary to a PAI-2 gene sequence, wherein the sample comprises a PLCG1 gene sequence and a PAI-2 gene sequence, thereby determining the identity of one or more of the allelic variants.

52. The method of claim 51, wherein the probes or primers are capable of hybridizing to an allelic variant of a polymorphic region of the PLGC1 and PAI-2 genes, and wherein the allelic variant differs from the reference sequence set forth in of SEQ ID NO:1 and does not differ from the reference sequence set forth in SEQ ID NO:3.

53. The method of claim 52, wherein determining the identity of the allelic variant comprises determining the identity of at least one nucleotide of the polymorphic region of a PLCG1 gene and at least one nucleotide of the polymorphic region of a PAI-2 gene.

54. The method of claim 53, wherein determining the identity of the allelic variant consists of determining the nucleotide content of the polymorphic region.

55. The method of claim 53, wherein determining the nucleotide content comprises sequencing the nucleotide sequence.

56. The method of claim 53, wherein determining the identity of the allelic variant comprises performing a restriction enzyme site analysis.

57. The method of claim 53, wherein determining the identity of the allelic variant is carried out by single-stranded conformation polymorphism.

58. The method of claim 53, wherein determining the identity of the allelic variant is carried out by allele specific hybridization.

59. The method of claim 53, wherein determining the identity of the allelic variant is carried out by primer specific extension.

60. The method of claim 53, wherein determining the identity of the allelic variant is carried out by an oligonucleotide ligation assay.

61. The method of claim 53, wherein the probe or primer comprises a nucleotide sequence from about 15 to about 30 nucleotides.

62. An Internet-based method for assessing a subject's risk for vascular disease, the method comprising:

a) analyzing biological information from a subject indicative of the presence or absence of a polymorphic region of PLCG1 and/or PAI-2;

b) providing results of the analysis to the subject via the Internet, wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease.

63. A method of assessing a subject's risk for vascular disease, the method comprising:

a) obtaining biological information from the individual;

b) analyzing the information to obtain the subject's PLCG1 and/or PAI-2 genetic profile;

c) representing the PLCG1 and/or PAI-2 genetic profile information

as digital genetic profile data;

d) electronically processing the PLCG1 and/or PAI-2 digital genetic profile data to generate a risk assessment report for vascular disease, wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease; and

e) displaying the risk assessment report on an output device.

64. A method of assessing a subject's risk for vascular disease, the method comprising:

a) obtaining the subject's PLCG1 and/or PAI-2 genetic profile information as digital genetic profile data;

b) electronically processing the PLCG1 and/or PAI-2 digital genetic profile data to generate a risk assessment report for vascular disease, wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease; and

c) displaying the risk assessment report on an output device.

65. The method of claims 63 or 64, further comprising the step of using the risk assessment report to provide medical advice.

66. The method of claims 63 or 64, wherein additional health information is provided.

67. The method of claim 66, wherein the additional health information comprises information regarding one or more of age, sex, ethnic origin, diet, sibling health, parental health, clinical symptoms, personal health history, blood test data, weight, and alcohol use, drug use, nicotine use, and blood pressure.

68. The method of claim 64, wherein the PLCG1 and/or PAI-2 digital genetic profile data are transmitted via a communications network to a medical information system for processing.

69. The method of claim 68, wherein the communications network is the Internet.

70. A medical information system for assessing a subject's risk for vascular disease comprising:

a) means for obtaining biological information from the individual to obtain a PLCG1 and/or PAI-2 genetic profile;

b) means for representing the PLCG1 and/or PAI-2 genetic profile as digital molecular data;

c) means for electronically processing the PLCG1 and/or PAI-2 digital genetic profile to generate a risk assessment report for vascular disease; and

d) means for displaying the risk assessment report on an output device, wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease.

71. A medical information system for assessing a subject's risk for vascular disease comprising:

a) means for representing the subject's PLCG1 and/or PAI-2 genetic profile data as digital molecular data;

b) means for electronically processing the PLCG1 and/or PAI-2 digital genetic profile to generate a risk assessment report for vascular disease; and

c) means for displaying the risk assessment report on an output device, wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease.

72. A computerized method of providing medical advice to a subject comprising:

a) analyzing biological information from a subject to determine the subject's PLCG1 and/or PAI-2 genetic profile;

b) based on the subject's PLCG1 and/or PAI-2 genetic profile, determining the subject's risk for vascular disease;

c) based on the subject's risk for vascular disease, electronically providing medical advice to the subject.

73. A computerized method of providing medical advice to a subject comprising:

a) based on the subject's PLCG1 and/or PAI-2 genetic profile, determining the subject's risk for vascular disease;

b) based on the subject's risk for vascular disease, electronically providing medical advice to the subject.

74. The method of any of claims 72 or 73, wherein the medical advice comprises one or more of the group consisting of further diagnostic evaluation, administration of medication, or lifestyle change.

75. The method of claims 72 or 73, wherein additional health information is obtained from the subject.

76. The method of claim 75, wherein the additional health information comprises information regarding one or more of age, sex, ethnic origin, diet, sibling health, parental health, clinical symptoms, personal health history, blood test data, weight, and alcohol use, drug use, nicotine use, and blood pressure.

77. A method for self-assessing risk for a vascular disease comprising

a) providing biological information for genetic analysis;

b) accessing an electronic output device displaying results of the genetic analysis, thereby self-assessing risk for a vascular disease, wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease.

78. A method for self-assessing risk for a vascular disease comprising accessing an electronic output device displaying results of a genetic analysis of a biological sample, wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease, thereby self-assessing risk for a vascular disease.

79. A method of self-assessing risk for vascular disease, the method comprising

a) providing biological information;

b) accessing PLCG1 and/or PAI-2 digital genetic profile data obtained from the biological information, the PLCG1 and/or PAI-2 digital genetic profile data being displayed via an output device, wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease.

80. A method of self-assessing risk for vascular disease, the method comprising accessing PLCG1 and/or PAI-2 digital genetic profile data obtained from biological information, the PLCG1 and/or PAI-2 digital genetic profile data being displayed via an output device, wherein the presence of a polymorphic region of PLCG1 and/or PAI-2 indicates a decreased risk for vascular disease.

81. The method of claims 79 or 80, wherein the electronic output device is accessed via the Internet.

82. The method of claims 79 or 80, wherein additional health information is provided.

83. The method of claim 82, wherein the additional health information comprises information regarding one or more of age, sex, ethnic origin, diet, sibling health, parental health, clinical symptoms, personal health history, blood test data, weight, and alcohol use, drug use, nicotine use, and blood pressure.

84. The method of any of claims 77, 78, 79, or 80, wherein the biological information is obtained from a sample from an individual at a laboratory company.

85. The method of claim 84, wherein the laboratory company processes the biological sample to obtain PLCG1 and/or PAI-2 genetic profile data, represents at least some of the PLCG1 and/or PAI-2 genetic profile data as digital genetic profile data, and transmits the PLCG1 and/or PAI-2 digital genetic profile data via a communications network to a medical information system for processing.

86. The method of any of claims 77, 78, 79, or 80, wherein the biological information is obtained from a sample from an individual at a draw station, wherein the draw station processes the biological sample to obtain PLCG1 and/or PAI-2 genetic

profile data, and transfers the data to a laboratory company.

87. The method of claim 86, wherein the laboratory company represents at least some of the PLCG1 and/or PAI-2 genetic profile data as digital genetic profile data, and transmits the PLCG1 and/or PAI-2 digital genetic profile data via a communications network to a medical information system for processing.

88. A method for a health care provider to generate a personal health assessment report for an individual, the method comprising counseling the individual to provide a biological sample; authorizing a draw station to take a biological sample from the individual and transmit molecular information from the sample to a laboratory company, wherein the molecular information comprises the presence or absence of a polymorphic region of PLCG1 and/or PAI-2; requesting the laboratory company to provide digital molecular data corresponding to the molecular information to a medical information system to electronically process the digital molecular data and digital health data obtained from the individual to generate a health assessment report; receiving the health assessment report from the medical information system; and providing the health assessment report to the individual.

89. A method for a health care provider to generate a personal health assessment report for an individual, the method comprising requesting a laboratory company to provide digital molecular data corresponding to the molecular information derived from a biological sample from the individual to a medical information system to electronically process the digital molecular data and digital health data obtained to generate a health assessment report; receiving the health assessment report from the medical information system; and providing the health assessment report to the individual.

90. A method of assessing the health of an individual, the method comprising: obtaining health information from the individual using an input device; representing at least some of the health information as digital health data; obtaining biological information from the individual, wherein the information comprises the presence or absence of a polymorphic region of PLCG1 and/or PAI-2; representing at least some of the information as digital molecular data; electronically processing the digital molecular data and digital health data to generate a health assessment report; and displaying the health assessment report on an output device.

91. The method of claim 90, wherein electronically processing the digital molecular data and digital health data to generate a health assessment report comprises using the digital molecular data and digital health data as inputs for an algorithm or a rule-based system that determines whether the individual is at risk for a specific disorder.

92. The method of claim 90, wherein the individual has or is at risk of developing vascular disease, and wherein electronically processing the digital molecular data and digital health data to generate a health assessment report comprises using the digital molecular data and digital health data as inputs for an algorithm or a rule-based system that determines the individual's prognosis.

93. The method of claim 90, wherein electronically processing the digital molecular data and digital health data comprises using the digital molecular data and digital health data as inputs for an algorithm or a rule-based system based on one or more databases comprising stored digital molecular data and/or digital health data relating to one or more disorders.

94. The method of claim 90, wherein electronically processing the digital molecular data and digital health data comprises using the digital molecular data and digital health data as inputs for an algorithm or a rule-based system based on one or more

databases comprising (i) stored digital molecular data and/or digital health data from a plurality of healthy individuals, and (ii) stored digital molecular data and/or digital health data from one or more pluralities of unhealthy individuals, each plurality of individuals having a specific disorder.

95. The method of either of claims 93 or 94, wherein at least one of the databases is a public database.

96. The method of claim 90, wherein the digital health data and digital molecular data are transmitted via a communications network to a medical information system for processing.

97. The method of claim 95, wherein the communications network is the Internet.

98. The method of claim 95, wherein the input device is a keyboard, touch screen, hand-held device, telephone, wireless input device, or interactive page on a website.

99. The method of claim 90, wherein the health assessment report comprises a digital molecular profile of the individual.

100. The method of claim 90, wherein the health assessment report comprises a digital health profile of the individual.

101. The method of claim 90, wherein the molecular data comprises nucleic acid sequence data, and the molecular profile comprises a genetic profile.

102. The method of claim 90, wherein the molecular data comprises protein

sequence data, and the molecular profile comprises a proteomic profile.

103. The method of claim 90, wherein the molecular data comprises information regarding one or more of the absence, presence, or level, of one or more specific proteins, polypeptides, chemicals, cells, organisms, or compounds in the individual's biological sample.

104. The method of claim 90, wherein the health information comprises information relating to one or more of age, sex, ethnic origin, diet, sibling health, parental health, clinical symptoms, personal health history, blood test data, weight, and alcohol use, drug use, nicotine use, and blood pressure.

105. The method of claim 90, wherein the health information comprises current and historical health information.

106. The method of claim 90, further comprising obtaining a second set of biological information at a time after obtaining the first set of biological information; processing the second set of biological information to obtain a second set of information; representing at least some of the second set of information as digital second molecular data; and processing the molecular data and second molecular data to generate a health assessment report.

107. The method of claim 106, further comprising obtaining second health information at a time after obtaining the health information; representing at least some of the second health information as digital second health data and processing the molecular data, health data, second molecular data, and second health data to generate a health assessment report.

108. The method of claim 95, wherein the health assessment report provides information about the individual's predisposition for vascular disease and options for risk reduction.

109. The method of claim 108, wherein the options for risk reduction comprise one or more of diet, exercise, one or more vitamins, one or more drugs, cessation of nicotine use, and cessation of alcohol use.

110. The method of claim 95, wherein the health assessment report provides information about treatment options for a particular disorder.

111. The method of claim 110, wherein the treatment options comprise one or more of diet, one or more drugs, physical therapy, and surgery.

112. The method of claim 95, wherein the health assessment report provides information about the efficacy of a particular treatment regimen and options for therapy adjustment.

113. The method of claim 95, further comprising storing the molecular data.

114. The method of claim 113, further comprising building a database of stored molecular data from a plurality of individuals.

115. The method of claim 95, further comprising storing the molecular data and health data.

116. The method of claim 115, further comprising building a database of stored molecular data and health data from a plurality of individuals.

117. The method of claim 116, further comprising building a database of stored digital molecular data and/or digital health data from a plurality of healthy individuals, and stored digital molecular data and/or digital health data from one or more pluralities of unhealthy individuals, each plurality of individuals having a specific disorder.

FIGURE 1

GATCTTCAAAGGTTGGGGTTTGATAGTGCCTTGAATAATTTTTAACTTTATATTGCCAGCGGAAGAAGCA
TTCTCTTTTTAGATTTAAAAAATGTAGATACAAATATTAGGGGTTTTATTTTTAGTGAAACATTTCAAAC
ATACAGGAATAGATAATTATGTAATGAACACTCGTATGTCCACCATCTGGCTTTGTAAAATCTTAAAATT
ATGTCTTATGTGCTCAATTGTTTTATTTCATAAAAGATACTGATAAACATAGCTGAAGTCACTTGTATAC
CATTCACCTTCTTCCCTGTAGATTACTATGAACTCGGTCTTTTTATTCTCATACATATTTTTTGTATTTT
TGCAGTATATTTATGTGTTCATAAACAATATGTAATTTTACAATATGTAACACACTAGTAACATACTAAT
TTAAAACTTGTTTTTAGTTTACAATATGTTGTAAACTATTGTAAGCTAAAGACATATTGTACAACCTATT
GTAAAATAAAAACAGGTTTTAGTTTTAAATTAGGTATGTTACTGGGATCATTCTGCAACTTGTTTATTCC
TCTCCAGCTTTGATTTTGTGGTTTTATTATCTTAACCTACACTTTTAATTAATCCATTTTATTTGTTACA
TGGTATTCTATTATATCATAAAAACTTATCTATTCTGTTGGTTTTTGTTGTTGGTCATTTGAGACCATGT
CTTCGCTCTGTCACCCAGGCTGGAGTACAGTGGCGTGATCTTGGCTCACTGTGACCTCTGCCTCCCGGAT
TCAAGTGGTTTTGGTGCCTCAGCCTCCTGAGTAGCTGGGATTATAGGCGTGTGCCACCATGCCCAGCTAA
TTTTTGTATTTTTAATAGAGACGGGATTTCACCATGTTGGCCAGGCTGGTCTTGAACTGACCTCAAGTGA
TCTGCTCACCTCAGCTGCACAAAGTGCTGGGATTACAGGTGTTAGCCACCATACCCTGCCTCTATTCTCT
TGTTAAGAGGCATTTAGCATGGTTATACAGTCTCTTGCCCTCATAAACAGTGCTGGAAGAAACACATGTT
TCTTGTGTATATGAATGAAAATTTGTTTTATACATTAGATATTTCCAAATTGTTCTCTTAAGTACTTCAG
TTTACATCATTACTCTCCTCCTCCCTCCCCTCCCACCCCCACCCACAACAGTATTCCTCTTTTTCCATAT
CCTTGCTAATGTTTCTAAAGTTTTGCTTTTTACATTTGGGTCTTAGATCCACTAGAATGTATTTTTGCAT
TGGGATGAAGTTGAAACCTAATATATTTTCCAAATGAGTAAACTGTTGTCACAGAACTATTTAGTTGTAT
TACCTCCTCTCTTGTATATCAGATATATCTACATATATGTCAGACTGTTTCTGGGCTGTCTGTCCTCTTT
AATTAGTTCGTGTATCTGTTTCTGCATCAGTAGCATACTGTCTTAACTACTGTAGCTTTATAAAGTCTAT
TGAGTAGGACAAGTTTGTTTCATTCTTCAAAATTGCTTTGGCTATTCTTGGCCCTCTGCTGTTTCATATT
AACTTTCAGATAAACTTGTCAAATTCTAATGAAAACTGTTGATAAACTTGTTGATTAACAAATTCTAATA
AAAACTGTTGAGATTTTTATTGGAATTGCAATACATTTATAGATTAACGGAGAAAGATATTGACAATACA
ATTGAGTTTCCAATTCACGAACATGTTATACCTCTCCATTAATTCATGTCTTTTGAATGTATCCACCAAT
ATGGTTTTGTAATTTTCTTCATAAAGGTTTTACATTTAAAAAATTCTTATTTTTAAGTGATCTTATAGTT
TTTATTGCTAATGTGAATGAGATTTTTTTCCATTATGTTTCTGTTGGTTATTCCTGAAGTGGTAATGCTT
ATAATTTTGGGGTGTTGGTCTTGTATCTGGCAGCAGATACAAGAGGTGCTCAGAGTTGTTCAGGGTTGCT
GAACTCTTAGTTCTAAAAGTGTCTGTCATTTGGGGTTTCTATGTAGATAATTTAATTATCTATAAAAACA
GTTCTTCATTTTCAGTTCATATATTTCATATTTCTTTAAGTTTTAATTTTTATTTTTAAACACAATTATC
CATAAAACCCTAACCCTTTCCCTAGTCAACAGCAGTCACAGCCAAATGTTTTATTAATTGCTATACTCAG
TGTTTCTTGTATCTCATACCTTCTGGGGTTTCTTGTCTTGTTGAAATACACCCTTTAATGTTTCTTTAGT
GAAGACCCAACAGTGGCACTCACTCACCTTTGTTTACCTGAAAATTTCTTTATTTTCATCTTAATTCATA
GTCTGTCTTTTCTCCAGTCAAGGAAGTGTCTTATAGGGAAGATTCTGGTTTCACTATGCTGTATCCAGGG
ATATATATGTATTTATAGATAGACTTTTAATCTGAGGACTAATGTATTTTATCCTACAGTATTACCAATC
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GACACTTTTCAATCTAGACATCTTTTTTAAACTATATTTTCATACTCTTTGTCTCTTTAGGTCTGATTTT
TTAAGTTCAGGGGAATATTTCATTTTGGGTGAGTTGTAGCACTCACTTCCAATTCACTAATTCTAATTAT
ATTTAATCTACAAGTTATTCCATCTATAATTTATTTCAATTACCACTTTTTGTTTTCAAAATTTCTAATT
TTATATCTGATTTTGTTTCATTTTTGTTTTATAATTTCATGTTCTTTCTAGATTTTACATCTTTTTATGC
ATACTAAACATACTCACTTGAAAGTCTTTGTAAGATTGTTCTATAAAATGTTACCTGAAGTGAATTCATG
TGCTAATTACTGTTGGCAGTTTTTCTGAGCCATTTTCCTTGTGTCTTTTGAAATTTCTGTTTGTAAGCCC
TTTTAACTGGGAGGTGTTTTTTGCTTATGTACTGTTCTCTTTTCTTTCCCTTCTTCTCCTTCTCTGTTCA
TTACTTTTTGTCTTGGAGGGAGTCTCTTAGCCCAGCTCAGCCCAAGCTAATAAGGCCCCTGACTTCAAGT
CCCCCCTTCTTGCATGGAGCAAGAAGTGATCCTCCTGTCTCAGCCTCCCAAAGTGCTGGGTAGGCGTGAG
CCACCACATCCAGCCTAGAGCACTTACATTGCTACATATTTGGAGCAAACATAATTAAAGTATGACTTAC
TGTGACCCAGCAGTCAATAACAGATATGTTTTTGTAATAGAATGTTGAAGGGTGGTAACTGGTGGTTTTA
CTTCATGGAGGGCTTTAGGTCGGCTATATGGGAAGCTGCCATCATGATGCTTTTGTTCTACACATTTCTG
CTCAGCCTCCAGAGATGTCTCCTATTCTAAGAGTCGTCTTTGTTTACTCTTGTGTCTATATTTTACTTAC
TTAATTCCCTCACATAATAGTGTATCATTGTATCCCATCTGTGCTCTATCAAGAAATGTAGCACAAGCAT
GATGTGAACTATGAATTTTCGACAATTTAAAAAATTAAAGGAATCATTCAGGGGTAAAAAGCACAAAGTT

FIGURE 1 (continued)

GTAGAACAGCTGAAGTGTGTTCTTTTTATGTATCCTGTCTTTGCCCCCTTTCTGGAAACTTGGATTGGCC
TACTTGCAGTCACTGTCACAGTTACACTACTTCTAGCCTCAAAGGTCATTGAAAGGATTGGGATTTTTGA
GAACCACAATAACACTTGCTCTAGGTACTGAAAAGGTTGTCCTGAACTCATTCATATCTTTTTATGTTCA
TCCCAGTTTGTTTTTGCTTTTCCCCCCAGGATTTTGATTACACAGACATCTTGCAAGCATATTTCCATTC
TTTCTCTCCCACTCTGTGCCTGGTGCCCGTAGGATCTGAAATAGCATTGGAATGACAGCTAGCCTTCTGG
AACCTGCAGTTTCAACCAAAGAAACTCTGATTCCAGATAACCCAGGAGTTTCTTATCCTGCATAATCTAG
GAGTTTACAAAAAGGCTGCTTATGGGTACTCACTGCTAAGTACAATCCACTGCCAAGTTTGGAAGCATTA
CCTGCTCTCACAACCCAGGGAAAGTAGCCCTTAGTAAAATTCAGGTTTTTTCAAACCAGCCTTAACCTTA
CAAACAGAATTTATCATCATGATTTTTCTTTCAAATGCAGTACAGCAAACTTTAGGATCAATGTTGACAT
CGTATTGCGTTTAGTCCTGTTAAAATACTCTCAGTGCCAAATACACACTTCTGCCTTTTTTCTCTTTAGA
GTCTAGAATTCTGTGGGGTTCCAAAAATGTATGTGCTTACAACCTTTTATATGTAACCACCTAGGGATTA
AAGGGCTAAATGTGAAGGAAAGTATCTTTACAATATTCATCTTGGGAAGCTCTCATTTTGGTGAGTTCTA
TTAGAGAAAATAAGACACAAGCTCATTAAAAATATATATATATTCTGAGCCTGGCATCTTGGTATAAAAT
TCAAAACGTTTTAAATCTATTTATTAGTAAGACTAACATAGACCTAAGTGTGAAGACTAAAATATTAAAG
CTTGTAGGTGATATCATGGTTGAATATGACCTTAGAGTAGATTCCTTAGGACAGAAAAACACCAACAAGA
GAAACAATTGACTAAATGGACTTCATTAAAATTAAAAATTTATGTTCAACAAAAGACACTGCTAAAATAA
ATACAGAATTTACAGACTAAAAGAAAATATTTGCAACATGTTTATCTGAAAGGGCTTATATCCAGACTAT
ACAAAGAATTCCTGTAGCTCCATAATAAAAAAACAGACATCCCATCCGCATAATAAAAAGAGCAAAAGAC
TTGAACATATACTATACAAAAGAAGATACAGGAATGGTCAATAAATAAGCAAATGAAAGAGTGCTCGACA
TCACTAATTATCAGTGGAGTGAAGATTTAACCACAGGGAGATACGAATTCCAGTTCTAGGTATTTTTACC
TCAAGTGAAATAAAAACATTTATCCATGAAAAAACTTGTACAAGAATGTTCATAGCAGTGCTCTATTCAT
AAGAGTGCAAAACTGGAAACATCCCAGAATAGATAACACATTATGGTATAGTCATAGAATATACTATATT
TATCAGCAGTTAAGAAGGGAACTACTTATGTATTCAACAACATGGATGAATCTTAAAAACATGGTTAAGG
GCCAGGTGCGGTTGGTGCATGCCTGTAATCCAAGCACTCTGGGAGGCCAAGGCGGGTGGATCACTTCAGG
TCAGGAGTTCGAGACCAGCCTGGCCAACATGGCGAAACACCGTCTCTACAAAAAAATACAAAAATTAGCC
GAGGGTGGCGCACACCTGTAATCTCAGCTATTCAGGAGGCTGAGACATGGGAATCGCTTGAACCTGAGGG
GTAGAGGTTGCACTGAGCCGAGATTGCATCACTGTACTCCAGCCTGGTGACAGAGCGAGACGCTGTCTCA
GAGGGAAAAAAAAAAAGTTAAAAAGGCAGACAGAGGAGTCTATATTGTATGATTCTATTTATATAATCTAG
ACTAGGCAAAATTTATCCATGATGATAGTAATCAGATTGAAGGATCAGTGGTTGCTTGGTGGAAATTGAC
TGAGAAGGGAAATAGTCATGTAAGAATACTGGCAAATGTCCTCTTCCCCATTACAAACGTCTGAGAAAGT
TACTAGAAAACAGAATCCAATTTGCCTTCTCACCCCCAACTTTGTAATCTTGAATCCAGATCCTGATTCC
ACCCAACCACTCTGCTGAATGGATAGCAGCTATATTAGAGAGACAATATAGTGGGCCTACTAGTTTTAAA
AAGTCATCCAAAGAATGTCATCTACAATCAGTTAAATTAGATTTTTACCCATTACTGAAGTGTGATTGAA
TTAGGGAAAGAGGAGAGGTGGTCAAAGGCAGCCTTCTCCAGTGGATTCCTTGTCTTCTTGAGATGGTTTT
GTGAGACCTTGCCTGGAAGACCTAGGTGGATAGTTTATTTTCTAAAAGTAGTCAAGAAAGCTTGTTCAGG
GCATTGAACACTGCAGGGACAAGCATACTTCTTGGAGGCCAGCCATCTCCTGCTGGATCTAAGCGGGGTG
GCTTCTGCCTCCACCTCCATCTCAGCTTATTTGAGAGAATCCTAGATCCTTGGTGCAGAAGCCCAGCCAG
CCTGTGAAGAAAAGTTGGTCTGGTAGTATCCTGTGAATGACGTGCGGGTTGGGTTTTTCTAAATCTCGTT
TACCTGACTCCTACCTTACATTCCAGTGGTGTGACTAAGGAACTGAGCAAACGTAACCCTAGGGGACTTT
GAGACAGGCTTTGGTAGTCCATGTGCACTAGAGTGAGGGGAAAGAGGCCACTCCAGAGTTGGGTACTCTA
CTGTTGAAGGTGAGCCTTTTGTGTCCAATTTTTCCGTGCATGTGTAAGAACAGTTGTCATGGAGATTTAC
TACTGACTTGTGCATGAGGACAGCTTATATCTCACCTTTTCTTATTCACCCTGTTAAATGTCAAAATGTA
CTAAGACTTAGGTATTTTTTCTGTGTCACCAACTACTAAATCACCCACCCATGATAGCAGGTAGTTACTG
AAACTCTTGTAGCCAAACAAGTGCATAACACTGGTACACATGATGTGAGAGTGCAGATGACTCCTTAGCT
TAACTGTGTAAGCTTTTAATTTCTGAGTACTTTTAGGATTGAGAAGTGGAAGACATTCTTGCTCTAGGTA
TCTCATGCTTCTGCACACCCAGAAGGCTGGTTGCGCCCCCACCCCACCCCCCGCCCCCTTTTTTTTTTTT
TTGATAGGGTCATGCTCTGTTGCCCAGGCTGAAAGGCTGGTTATCTTCACCACAGGTCTTATGTCTCAAG
GACCACGGGTCCACGTCATAGTCAGGAACCAGGCATGTGTGGGCAGAAATCACTACCACTTTCCTTTGTT
GCGGGTGGGGAAATTAAGAGCAGAGATTCTTGGATTCTTAAATTCCTTCTCTATGTTTATGTCATCTAGT
CTGTTTTATGCTGTTTTATGTAATTCCCTGCTTCTGGATTTCTTGAATTTTTTTCCCCTTCTCACTTGTC
ATAATTGGCTCTTGCTTGTGAGTCTATTTTCATTCAGCTTGGTAGCAGAAGTCTTCTTCACTATTGTTTA

FIGURE 1 (continued)

GATTCAGTTTTCACATGGTTTTAGTAACCCTTCATTGGGTTTAGAATCAACTTTTAACCCTTCCACCAAA
AGCTCTTATTTTTTTAAAGGCTTCCCAGAAACATAGTTTCTCTCAATCTCATCAAGAAATGCTTTTAAAT
GCAGAAGTTAGAAAATGGTGAATAATTATGGCTGTTCCTGGAAGTCATTGTGTCCTTAGTAATTACATGT
TGTAGTCTTTGGTTCTGCTTCTTTGACAGCTCCACCACACTGTAATTTAATGGAATTCACTTAGATTTAA
TGGAATTCAGTCCTGGTAGAAAACTGCTATTGGGTCACAGAGTTGGCAGCAAGGCTGTGAAATTGATGTG
GGAATGGGGGTGATTATGTGCTTTGTGTTGACAGAAGTTAGTTTTTGGGACATCCCATGTGGGTTTTTCC
CAGGAACATAAACATTTTAGAGAATTAGAGCTAGAAACTTTCTTCTGGGAAAGCCTTAGAAGTCAGTTGT
GCTTGGCAGTGAGATGGGACAATGTGCATTCTTAACAGGTTAAATGTGCCAAACTCTCTCTTCAGTACTA
TTCTTTTTTACGTTTGCTTAAGGTCAAGTTCCTGCTCTTTTGTTCAAAGTCTTGCTTTGTCACCCATGGT
GGAGTGCAGTGGCGTGATCTTGGCTCACTGCAACCTCTGCCTCCTGCGTTCAAGCAATTCTTGTGTCTTA
GCCTCCCTATTAGCTAGCTGGGATTATAGGCTTGCGCCACCTTGCCTGGCTATATTCAAAGTCTGTCTTT
ACTACACTGTCCCAAAGTAATCTACATTTGGGTTTGGGTCTTTACAGGGTGAGAAGGACTGGCAGAAATA
CGAGACTGCTCGGCGGCTGAAAAAATGTGTGGACAAGATCCGGAACCAGTATCGAGAAGACTGGAAGTCC
AAAGAGATGAAAGTCCGGCAGAGAGCTGTAGCCCTGTACTTCATCGACAAGGTGAGAGCATCTTCCCATC
GGCATTGTCTAGTGTTGAGCTTAACAAAGGGAGTTTCTGCTCTGCCCCAGGCCCTGTGCCACATACTGTA
TATCACAACTCAACATACATATATTTGTATGTAAAACTGAATCAAAAGTTGCACAAAACAATGCTTAGCC
TTACTGTGAGCAGTAGATTCTGATCTTTTTTTAACTCTATTTCATTCCTTTAGAAAGTTGGTTATAACTT
ATAAAATTGTTTAAATAAACCATGCAGGTATCACCATTATATAGTTTTAAAGACCACGCTCTAGAGGAGA
TCAATTTCTTGGTACTCACGAGAAGAAAAAAAAGTTCATGTTTTTCCCCCAGTCTTGTATTTTAACATAA
GTTCTGAATTGTCTCAAAATTCACACTAGCTTTTTGAGTTTGATTGCCCAGAGTAGCAGCACTCCCTCAT
TTGCTGCCTTATTTAATTTTTTTTTTCCTTTTCTCCATCCCTATTTCAGAGGACAGAATAGAAAGAAAAG
GAGCATGAATATTTAACATCCCTATAGATTTCATAGTGAGTGGGGGAGGAAGTAACACTGCAGAATCCAG
AGTTCCCAGGCCATGCTGACTGATGCTGTGGCTTCAAACAGAATTGGGAGGCTTCTGTTTTGGATGCCTA
GAAATTGCATAAGGGTCAAAAGGCTGGGCGCAGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCA
AGGCAGGTGGAACACGAGGTCAAGAGACCATCCTGGCCAATGTGGTGAAACCCCATCTCTACTAAAAATA
CAAAAAAAAAAAAAAAAAATAAAAATTGGCGTGGTGGCGGGCGCCTGTAGTCCCAGCTACTTCGGAGGCTG
AGGCAGGAGAATGGCATGAACCCGGGAGACGGAGCTTGCAGTGAGCCAAAATTGCGCCATTGCACTCTAG
CCTGGCGACAGAGCGAGACTGTCTCAAAAAAAAAAAAAAAAAAAACACAGAACGAAATTGTGTAAGGATC
ATGTCTCTTCCATTCATGCTCATCTTTTCTTTCTTTCCTGGGCAGCTTGCTCTGAGAGCAGGCAATGAAA
AGGAGGAAGGAGAAACAGCGGACACTGTGGGCTGCTGCTCACTTCGTGTGGAGCACATCAATCTACACCC
AGAGTTGGATGGTCAGGAATATGTGGTAGAGTTTGACTTCCTCGGGAAGGACTCCATCAGATACTATAAC
AAGGTCCCTGTTGAGAAACGAGTAAGTTAATGTACCTGTACTGTCTGACTTGTTTTCCATTATTCAACAA
GCATGGGTTGACTGCTTTTTTGTGTGCTTTGCACTTTGCTGGGCACCAGCAAAAGTGACTTGAGACAGGC
AACATGGCACATGCCTGTAGACCCAGCTATTCAGAAGGCTGAGACAGGAGGATCACTGGAGACCAAAAGT
TTGAGGCTGTAGTGTGCTGTGATCACACCTGTGAATAGCCACTGTACTCCAGCCTGGGCAAAATAGTGAG
ACCTTGCCTCTCATATTAAAATAAATAAAAATAAATGACTTGAAAGAGGGGAGAGGTATTATTTGATATC
TTGTGTACCTCCTTTTAGTCACTGTTCCGCCCTGTGCTACCTTCCTGGTAAGGAGTGGCCTTCTCCTATA
GCAGTATTCAATGGAGCATGCTGTAGAATAGGCCCTTAGAGCAAACTCAGCATATGATTTAACTATATCT
TAGTATCCCCTGGTCATGTGGTACATTTGTCACTTTTCATCTTTGCTCAGCCTTTCTCCAACTCCTGACT
GAGTGAAAGGTTAATGTTAGTCCCCAGATCTCTGAGCCCATCACTGAAGAGGGTACTATAGCTCTGTAGT
CCCAACCTAATCTTTTCCATAGTATTGGGCTTGAACCAGAGACTTACAGTGTGCAGGATCCTAATAATCC
AGCCCACCAGCAGTCCTCTTCTTATAAAGACACCTCTTCTCATAAGGACACCATAATCAGTAATCAGGTT
TTGCTGGCTGTGGAAGTACTCTGGACAGATTAGATAACAGTATGTATCAATGTAAATTTTTGAAGCTGAT
ACTGTGTAAATGTAAGGGAATATCTATTTTTAGAACATACACACTGAAATGTTTAGGACCATATTATAAG
TAAGTACTTATAAATGTACTTTAGGACCATATTATAAGTAAGTACTTATAAATGTACTTTAGGACCATAT
TATAAGTAAGTGCTTATAAATGGCTCAGAACAAACAATTATGTATATATATCTGTAAATATACACATGGA
GAGAGTGAGCATACATGCACACTGTGCAAATGATGAATGGGGTAAAATGTTAACAGTGAATCTCGGTGAC
GGATGTATGCGTGTTCCTTGTGCCTTTTTCTTTGCAAGTTTCTTTAAGTTTGGGGTTATTTCTAAAGTTA
GGATTTTTTTCAAGAGTAATAATTAGGATTCACTTATATCTTTTAGGTTTTTAAGAACCTACAACTATTT
ATGGAGAACAAGCAGCCCGAGGATGATCTTTTTGATAGACTCAATGTGAGTAGATGAAGCACACAATGTT
GAAGGGAGTCCCAGCCAGAGCCTCACAGTACCTAAAGGGGAGGGTTGCTGGCAGATGACTTGGGCTCTCC

FIGURE 1 (continued)

CTTTAGCCTGGCCTGCTCTGTGGCATCCCATACACTCTCTCTTCCTCCCTCTGAGTCCACGGTGAATCTG
TAGTCAAGAGAAGACACATCTGCTGCAGAACAACTGCTAAAGCACTCAGGGTGGGGGGTAGATGAGCCCT
ACCTTTTATCCTTCCCTGCTCCTGCAGAGCTTTCCCTTCACTGAATGCCCAGCCACCCCTGCTGGAGACC
CAAAACCTGTCCCTGATATCTTAATAGGGAAGGAAAAATTTGCTTTATTGGTTTGTTAAGCCCACCAACC
TGGGCCAGGCTTGGTGGCTTACGCCTGTTATCCCAGCACTTTGAGAGGTCAAGTAGGGCAGATCCCTTGA
GGTCAGGAGTTTGAGACCAGCCTGGGCAACATGGCAAAACCATTATCCAGGTGTGGTAGTCCACACCTGT
AGTCCCAGCTGCTTAGGAGCCTCAGAAGGATTGCATGAGCCCGGGAGGTGGAGGCAGCAGTGAACCGAGA
TTGTACCACTGCACTCCAGGCTGGGTGTCAGAGTGAGACCCTGTCATACACACACACAAAGATTGAAATA
CTTCATAGAGAGGCATCATGTAACCCTGTATTCTGGAATTCTTTTCCTCTTTCCCTAACTTCCCACTTGT
AGGGCCATAAACTTGACAAGATTGTGACTGCACTGGCATAAATTACTCCTAGGGCTGCCAGAAGGAGCAG
GTAGTATAGCTTTGACCTAAATCTGTTGCTTTGTCTCCTCCAGACTGGTATTCTGAATAAGCATCTTCAG
GATCTCATGGAGGGCTTGACAGCCAAGGTATTCCGTACATACAATGCCTCCATCACGCTACAGCAGCAGC
TAAAAGAACTGACAGCCCGTAAGTATTGCTTGGCCAGATAGGGCCCACACCCCTACTAATGGTATCCGGT
GACCTTGCTTATCTAAGGCCTAGAGTCAGTTCTACTTTTTTTCCCTACCATTGTGGTCAGACACTTTTTC
CCTTTAGACCTCTAGTAGCGAGATAATGCTTTGTTGTATAAACATAGGATCAATGCTGTTTCCCCCTTCC
CACCCCAACTTCAAGATTAATTTCATGGAATGCTGACAGCTTTTCACCTGCTACAAAAATGCCTGCATTT
GTGTTTTATACATATATTACTTAAAAGCCCACAGAGTGAAGACAGTGCTGTGATGTTCTGTTAAATTGGA
GAGAGTAAAGTTGTCATGGTTACCAGAAAAATACAGGAACAAGTCCTTTCCTTGAGGTTTCTGTCATTTT
TTTCCCATAAGAGAGTAGATACTTTCTATAGCTGATTTTTAGAATATTATCACCAAGATCCACGGGCTTT
TTTTTTCCTGGAGCCCAGTCACTATTGAATTTCCACTGCCCTCTGTAAATACATCAGATGGCCTTAGAAT
ATGAACCAGAAAAGCCAGAGGTAGGTATGTTGAGGGTCAGTATTTTAAGGTGGTATAAAGAATGCCACAC
TATACAAATAAAAACAATTTTTTTGGATGGCATTTTTAATTTTTCTTTTTAAATAAGATACTACCAGGCC
ATGTGCAGTGGCTCACACCTGTAATCCCAACACTTGGGTAGCCGAGGCAGGAGAATCACTTGAACCCAGG
AGTTCCAGACCAGCCTGGGCAATGTAGTGAGACCTTGTCTCTACTAAAATTTCTAAAAATTAGGCAGGTG
TGGCGGTGTGCACCTGTCATCCCAGCTACCTGGGAGGCTGAGCCCAGGAGTTTAGGGCTGTAATGAGCTA
CGACCATACCACCGCACTCCAGCTTGGGTGACAGGGTGAGACGCTATCTCTAAAATAATAATAATAACCA
TAATAATACTACCAACTGTGGCTTAATTTTTTTTTTTTTTTTTTTTTTTTTGAGACGGAGTCTTGCTGTC
ACCCAGGTTGGAGTGCAGTGGCGCGATCTCGGCTCACTGCAAGCTCCGCCTCCTGGGGTTCACGCCATTC
TCCTGCCTCAGCCTCCCGAGTAGCTGGGACTACAGGTGCCCGCCATGTCGCCCGGCTAATTTTTTGTATT
TTTAGTAGAGACAGGGTTCACCGTGTTAGCCAGGATGGTCTCGATCTCCTGACCTTGTGATCCGCCCGCC
TCGGCCTCCCAAAGTGCTGGGATTACAGGTGTGAGCCACCGCGCCCGGCCAAAATTTTTAAACTTTTAAC
GTCCCTTCAATTCCTCGTTCTGTTCTGGCTACATTGGGTGGAGAGGTGGGGAGGTAGGAAGTGGCCAGTA
TAGAACTTATGAATATGGGCAACAAACCATAGTAATATCAGCAGCACCTATGATGAGCATATGGGTGGGG
AGGAAGCAAGGAGATGAAGGGTCCCTAGCCAAGTTCCCTGAGTAAAAAGAAAGGTGTAGATTTTATTATA
TTACCTAGACTCAGAGTTCCTCTTGTGATAGGAATTTACCCAGGCCAAGCTTACATATAAACTTCCTACT
ATCATTTTCTTAAGACTGTTGACTCAAATTTTGACCTTAGTCCTTGGGGGCAATTTGAATTAATCATCTG
AGTAAGATAAGAGCCAGCAAAATCATGGGGACGAGGCACTGGGGGAAGACATACTGTGTGTTCACTTTTG
GTGTACAAACTGACCCTCTTGCTACCATGTTCCTTTCTTTACAGCGGATGAGAACATCCCAGCGAAGATC
CTTTCTTATAACCGTGCCAATCGAGCTGTTGCAATTCTTTGTAACCATCAGAGGGCACCACCAAAAACTT
TTGAGAAGTCTATGATGAACTTGCAAACTAAGGTATCTTGGATAAAATGAAGGGAACTGTGTCTGCTGTG
GGCAGATTATCTGCGAATGAGAGGATTCAGGGCTGAGATATCAGCAGGCCAGTGCTGGGTCTGTTGTAGA
AGGTCTATGCTAAAGATAAACAAATGGAAATATGATAGTAGTTAATCTCTGATCAAGATACTGAATATCA
GAGTATCCATTATTCAAGAAATCTTTATTCTACGCATAGAAGTTCTATACTGGCCACTCCCTATTTTGAA
AAACTAACTTTGGTGTACATTCTAATTGCTAATTACTGTCCTTATTGTACATGAGGAAAGTGGATTTAAA
GAGAGTCTTCATAATTCCTTGCTACAGCCCAGAAATACAGCCATTTCCAAATTAGATTGTTTCAAATTGA
AAAGATGATGAAACAATTATATATTTAAAGTCTTTCAAATCCTAGCATAGCTATTTTTATTTTTACGCAT
TCCACATGAATCATATTTTTATATAGTTCATCATCAAACATCTGTTGAATACTGGCCGTGTGCCAGACAA
CTTGCTGCCCTAAAGGGAAAGACTGGTGTGCAAATAGGTGCTATTCCTTGTCCCTGAGCCTCTTTCCTCC
TCCTAACTCCGCCTGGTACTGAGCTTTTAAACCATAAGGCACTTAACATTTGATGATGAACATTTTTGTG
TTAGCAGTGACTTCATAACTAATTCATCCTAACATGGTGGTCCACAGTGAGAATTTGCAGATATTTCATT
ATAGAACAGATACACAGGGTTAAAAAGGAAACAAATTATATTGAAATACAGTTATCAAAATACATTTTAA

FIGURE 1 (continued)

AGTCCGATAATAGATGTGCTTCCTTATTAAGGTCTTGAGGTGGCCTGTAGTAAATTTCAAGGTAGTAATT
AATTAATATCAATGATACTTTAAGATTTCTGCAGCAATTCAAATATGAAATGAAGATGTCTAACATCTAT
TGATGATAAAGTCATAAGTGCTGCTGCTATTACTATGGTTTGTTCCCCATATTCATAACTGAAGAAGAAA
TACTAAATTTCAGCTAGAAGCTGGGTGCAGTGGCTCACACCTGTAATCTCAGCATTTTGGGAGGTTGAGG
TGGGAGAATCACTTGAGCTGAGTAATTCAAGACCAACCTGGGCAACATAGTGAGACCCTGTCTGTATTAA
AAATTTAAAAATAAATATAAATAAGTTCCAAAAAGAGGTTATTGAAATTATAGATTTTTTCTCATCCAAG
TTCATGGAATTCTATACTTGTACAACTGGAGTTTAAGAACTACTACTGTGGAATGAGACTGCATTTTAAG
GCCCAGAATATTTTCCATTTGTTGAGATTTCCTTAAGATAAGTACCCATGAGTAATATAGCTGGTTCAAA
AGGTACACACAACTTATAATTTATGCTACAGATGCCATCTGGCTTTCTTGAAGAGACGTACATGTCCACA
GTGAATGAGTATACATCCATAGACCTTTGATTCCTTGGATCATATGATTGGCAGGCAAAGAACTCTATAG
ACGGCCCATCCTAGCAGCTCACATTTGCTGCCACTCTGTTAAATGCTGGTCATCTGGAATTGTTTATTCT
CCTCATGTTATCATTACAAGCCAGAAATAAAAGCATGAATATTCAGGTGCTGTTTACCTAATTCAGGAAA
ACCCCTCCCAGGAGCATGAGGAGGTCTTTTGTTGCTCTCGCTCTGGAACCGGGTTTGGGCAGCCCAGGCT
GCCTGCCAGATGAGCCCTCCAAACCCAGGATTCCTCTCCTGTGTGCCCACAAAGCAAACACACGCCCCTG
TTTGCCAAGTGAATCAATGGAGTCTTTGATGCTTTGAGAGAATTTGACATAGCCTGCCAATTTAGCATTC
ACAGAAATGGTTAAAAGATCATGGTTTGCTACATTTCTATCCTAAAAAGAATCTGGCTAGTGGTGTCTGT
GATGCTTTTGTATATAGAATCAGTCCCCTCAGTTTGGCTTTGGACAACATAGATGTTGGAAGTAAGCCAT
TCATAGTAAAACATATTTAGTGATCCTCTCACAATGGTGGCCTCTGTTTCCAATCTTGGGCTGTGTGTAT
CTAACAACAAACAATTCCAGGTTCAGTGAGCAGCCCAGTGTGTGTCAGACATGTTATTTACTCCGTAGAG
GTTGTCTTCACCTCACATAGATGACCATAGGTATGGGGTTCTCCTGCCCTCTGAGTAGCGTGAGCTCAGT
GACAGGGGCTCTAGCTCCATGTTGTTATCCACTGCTGTCTCTAAGCAGGAATCTGAGAAGAACTTAGATT
CACCAGGGGTGCTTCAAAGATTCTAACAAGCAAGAAAGGCTGAAACTGCCCTTGTCTCTTCCCTTATAGA
TATGGATTCCATGAGAGTTCACATGGGGAAAAAAGCTCCACAGCTAAAAGTGTTTTCACATCCATTGAGT
GACAACTAAGGTCCTTCCCACCTCAGACTTCTCTCCTTTTTTTTTGAGACGGAGTCTCGCTCTGTTGCCC
AGGCTGGAGTGCAGGGGCATGATCTCGGCTCACTGCAAGCTCTGCCTCCCGGGTTCATGCCATTCTACTG
CCTCAGCCTCCCGAGTAGCTGGGACTACAGGCACCCACCACCACGCCTGGCTAATTTTTTGTATTTTTAG
TAGAGACGGGGTTTCACCGTGTTAGCCAGGATGGTCTTGATCTCCTGACCTTGTGATCCGCCCTCCTCAG
CCTCCCCAAAGTGCTGGGATTACAGGCGTGAGACACCGCGCCTGGTGACCGCTCTCCTTTTAAAAACAGA
ATGCCAAAGCTAAGCCCTGCCATGTCCTGGTTTGGGACAGACTGGCTGAGCTGTTTGGCTTCCTGGGTGT
CTTTTAATTGCCAGTTTGTAGCCCCTTGAGTACTCTCTTCAGTGCATCCATTTTCCTTGAGAAGCTGGCA
CCGCCTTCCCAGAGTACTGGTGGGATCTGAGGAACGAGCTGGGGTTGCCCAGTAGATGCAAGTATCCTGC
TTCAGTTTCCTAAAGAGGAGCTCCTACAGTGTTCTTAGAATGAAAGCTAAGAACTGGCACAGGATCTATT
TGATAAACAGCTGTCATTTGTAGCCATCCTCCCAGATGTATGACAGCAGAGTGTTCTCTGATGGAAAGAT
CAGCACCCAGATTCCCAGCCCCAGCGGGTTCCTTTCCCTGAGCCCCTAGGTTACTGCCCTGTAAAACCCT
TGTTTCTTTCCAGATCACTGAAGAACAAATAGTTGAATTCACTAGTCCTTGTGCATCTTCTCCCTGCCTT
CATGAAGCCACCCTTGTTTTTTTTTATCTGACAAACCACTGACAGAGACAGCCTGGTCCAGATAACATCT
TGGTTTCACCTTCTCAGGTGGAGCCATTTTTCCTCTACAGCTCATAACCTTACCACTATTATTTCCCCTA
GATTGATGCCAAGAAGGAACAGCTAGCAGATGCCCGGAGAGACCTGAAAAGTGCTAAGGCTGATGCCAAG
GTCATGAAGGATGCAAAGACGAAGAAGTATGTACCTGGTATTGTGAAAGTTGGGGCTGGTAGAGAAAAGT
GTGCAGCATCTGTCAGGGCCCCTGGGGCCCTGGCTTTTCGATGGTTTCTGAGAAATGTCTTTTGGAAATC
TCTATACTAGGGCTTTTATTGACTCAAAGTGGCAGGATGGGTACAGTGTGCTCTTGTCTAGAGCCCAGGC
CTGGTTCTTGAGGACTTTGCTATTCTTCTAGGGTAGTAGAGTCAAAGAAGAAGGCTGTTCAGAGACTGGA
GGAACAGTTGATGAAGCTGGAAGTTCAAGCCACAGACCGAGAGGAAAATAAACAGATTGCCCTGGGAACC
TCCAAACTCAATTATCTGGACCCTAGGATCACAGTGGCTTGGTAAGTGTTGAGCCCTCCTTGAGCTCCTG
CTGCTAGCTTAAGAAAGGTGGAGGGGGTTCCGAGAGCACTGGTGGCCTTCACATGCCATTCCTAAGCTAC
ACACTTTAGTCCTCTGGGGAAACTTCTGGCTTCAGCTGTGTACAAGTTACTCTGGTTGCTGAACCTTGTC
TGTAAATGCATTGCAACATTCTGGTTGCTCCTAAATGGTCAGTGCTGTTACACTGCCTTGTAGTGTATAT
TTTTAAGAGGCAGGTGCCATCCCTATTCCTAATGGAACTTTAGGACAGGAATGGAAACTCTTAGCTTCTG
GAAGAATAGGAAAGAGCCCATCCATCTCTACACTTCAACAAAACTTTTCGTTGAATTTTTTTGCAGTTGA
AGGTAGGAACAAGAGATAAAGATGAGAATACAGATCTGAGCAACTTACACAGAGAGGCAGAGGGACCTTT
AACAAAAGCAGATAAATACTAGGTTTCTCTGTGTGTCACACACAGTGTCACATAACATCTGAAACAAGTG

FIGURE 1 (continued)

GCTTTGTTATGGAAGATGTTTAGTTTGAGCTGTTAAGTTCTGAGCATAGGTGGAGATATCCTCCCCTATG
GCACTTGCTAGTCCGGGCTAAAGTTTCCATCTAGGTCTTTTGTACCTCTTTCTGCTCGTTTTGCCTTGTT
TGGTGCTAGAGATTTGGTTAGCTCTTAAAAGGCAATATAGTATAGTGGTTAAGAACATGGAGAAAAACTG
CTTGGGTTCAAATTTCAGGTCACTTACCAGCTAGCTGTGTGAGAAAATCAGTAAATTACCTAACGTCTCT
GCCTCAGTTTCATCTGTACGTTTTTCACTTGTACATCTGCAGAAGCACCTACTTTAGAGATCACTGCCAA
GATTAAATGAGTTGATCACATAAAACCTTTAGAACATGCTTGGTGCACTATTAATTTGCATCCTCACTAG
ACAGATGTGAAAGAGAAGATGGAACATCTGACCCTGGGCCTCAGATATGGGCCATTGCTGAGTCACCCTA
ATCCCCCCCCTTATTTCTCCTTTGTTTGCAGGTGCAAGAAGTGGGGTGTCCCAATTGAGAAGATTTACAAC
AAAACCCAGCGGGAGAAGTTTGCCTGGGCCATTGACATGGCTGATGAAGACTATGAGTTTTAGCCAGTCT
CAAGAGGCAGAGTTCTGTGAAGAGGAACAGTGTGGTTTGGGAAAGATGGATAAACTGAGCCTCACTTGCC
CTCGTGCCTGGGGGAGAGAGGCAGCAAGTCTTAACAAACCAACATCTTTGCGAAAAGATAAACCTGGAGA
TATTATAAGGGAGAGCTGAGCCAGTTGTCCTATGGACAACTTATTTAAAAATATTTCAGATATCAAAATT
CTAGCTGTATGATTTGTTTTGAATTTTGTTTTTATTTTCAAGAGGGCAAGTGGATGGGAATTTGTCAGCG
TTCTACCAGGCAAATTCACTGTTTCACTGAAATGTTTGGATTCTCTTAGCTACTGTATGCAAAGTCCGAT
TATATTGGTGCGTTTTTACAGTTAGGGTTTTGCAATAACTTCTATATTTTAATAGAAATAAATTCCTAAA
CTCCCTTCCCTCTCTCCCATTTCAGGAATTTAAAATTAAGTAGAACAAAAAACCCAGCGCACCTGTTAGA
GTCGTCACTCTCTATTGTCATGGGGATCAATTTTCATTAAACTTGAAGCAGTCGTGGCTTTGGCAGTGTT
TTGGTTCAGACACCTGTTCACAGAAAAAGCATGATGGGAAAATATTTCCTGACTTGAGTGTTCCTTTTTA
AATGTGAATTTTTATTTCTTTTTAATTATTTTAAAATATTTAAACCTTTTTCTTGATCTTAAAGATCGTG
TAGATTGGGGTTGGGGAGGGATGAAGGGCGAGTGAATCTAAGGATAATGAAATAATCAGTGACTGAAACC
ATTTTCCCATCATCCTTTGTTCTGAGCATTCGCTGTACCCTTTAAGATATCCATCTTTTTCTTTTTAACC
CTAATCTTTCACTTGAAAGATTTTATTGTATAAAAAGTTTCACAGGTCAATAAACTTAGAGGAAAATGAG
TATTTGGTCCAAAAAAAGGAAAAATAATCAAGATTTTAGGGCTTTTATTTTTTCTTTTGTAATTGTGTAA
AAAATGGAAAAAAACATAAAAAGCAGAATTTTAATGTGAAGACATTTTTTGCTATAATCATTAGTTTTAG
AGGCATTGTTAGTTTAGTGTGTGTGCAGAGTCCATTTCCCACATCTTTCCTCAAGTATCTTCTATTTTTA
TCATGAATTCCCTTTTAATCAACTGTAGGTTATTTAAAATAAATTCCTACAACTTAATGGAAACTTAAGT
GTCTGCCTCTTTGTTACAAAGGGCCTCAGGCCAGAGTTGGGGCTGGGACTTAGTGTGGGATGAGGTCTCA
CCACTCAGGTCAGCAAGAGTAGATTCCTCCCAGGAGCAGATGAGGCAGGGCCTGGCCTGGAAAGGAGTGT
TGTGTGCCTGTCCTGCTGCTGTGGGTGTGGGTTAAAGAGGATCCAAAGTCCATATCCTTAGATAAAAGAC
AGGAAAGGAAGGAAGGGTGCAAAAAATCCACAGTAAGAGGTGTGGTGCAAAGACAGCATCGGAGGCCTAG
CGTAGGTAAAGTATATTGAGCAGGATGTTGCAGCTGTATTTGAGTCAAAAGTTTTGGAGAGCTTTCCATG
TGTACTGGCCAGAAGCAGAAGGGAGCTGCTTTAGGTTTTTTCACGTGGCTAAGCTTACAATCAGGATGGG
GAGAATTAAGGTTCCAGATCCCAGAAGCCCCTTCCCACATGGGATGCAAACTTCTCCCTGCATTGACTGC
TTAATTGAAAAAGGCAGTGTGGTGTGGTCTCTGACCACTTTCTGGTGCTCCAGTTACCCTAGCTGGCTAT
GGTCTCTACAAAAATTGTTCCTTTGCTCATCCTAAATTATAGGTAAGTCTGGAATTCAGAATGAAAGTGA
GGTCTCTGTCTAGGTCAAATGGACTGCAGGGAGCAGGAAGGCCAGAAGGGTCAAAATTGGTAAATTAATG
GAAGGGCCCTGGGCCCTCTAGCTTGTTAGCACGAGCAGGTAGGTGTCTTCGGGGAGGCGAACCCATAGTC
TCTGTTCTCCCTGAGGCTGGAGGCAGGGCTGGTACTAGGCCCACAACAGAGAATCCTGGAGGTCCTTGGC
AGCCTGTATTTTTATTAACCAGTGAAAGAGGCAGCATTCACCCCAGGGAATAAGGGAGGTTATGTAGCCA
TCACTGCTTTGGAGCAGAGAGACTCCAGCCAGGTGTTTTTGAATTCTGTGTTGAGGTAGCTGGGCCACTG
AATGTAGGGAATACAACAGAGAGGCTCTTTTGGTACCCATTTGATACACTGTGGCTGGTAGGTAAGTAGG
TTGGTGTAAGTGGACCTCAGATGCCACAGCTAGGGGACAACCTTTGGTCCAAAACTAGAAGTCAGGTAAG
GAGGCCTTGCAGGCAGAAGACCTTGCTGATGAACAGGAAGTAATGCCTACCTCTCTGGCAAGGACCTCTC
TTGCAAGTCTGAGGGCAGATGCTGGGCAACAAGATGCTGCTCAACACAACTAAGAAGGGCATCCCAGACA
GTGGCAGCAGGCCTGGGAGACCAAAGCCAGAGAATGGGAAGCTGACCTGGCCACTGGGGATGAAAGAAGA
GGCTGAACAGGTAAGTGGGGGCCAGATGTAAAGGACCTTGAAGGATGCTTAACCCAGGAGTCAAGAATAA
ACTTATCCACTTGCCTAGTCCAGTAGGTTTTACTTCCAGCCACGTCCAAGAACAGGCCAGATGGGCAGGG
TCTGAGAAACTCCCTCCCATCAGGCCTTTCTATGATGCCCGAGTTCGGTGTGGGCAAAGGGCTTCCACGT
GCTACCCAAGCCAGATATCTCTGTGCTGACTTGGCTTTTCTCCTCTCTTACCTCACCTTCATCTCCCATC
CCCCAAATCTGGCCAGCAAGTCCTGTCTCTCCATTCTCCCTGCCAAAAGCTGTCAAATTTCAGACCTCTG
CTACATTAAAACATGAAAAGTAAAAAACCTTCACAACCCTCAGCCCTTTCCAGCCACTACCTTTCCCTTT

FIGURE 1 (continued)

TTTCCCAAACAAGCACCTGCAATAAGTCATCACCATCCAGTCATTCCCCCACCCACTGCAACTAGCTTCT
GTCCCATGAGCCCACAATTCCTTCTCTTCACTCTGACCAATGTCGCCAATGACTAGATAACCAAACCAAT
ACATGGGCTCTCCATTCTGCGTCTTAGAGTCTTTGTGGCACTGGACACTGTTGACCACTCCTTCCATCAT
TTTGAGGGTACGATGATTTTTAGCAACTTTGCTGAGTGGTGCAACTATTAACCATGTCAGTTTTAGAACA
TTTTCATCTCCCTGTAAGATCCCTTATGCTCATTTACAGTTAATCCACATTCCCACTCCCGGCCTCCACT
AACCTTTCTAAATTTGCATTCTGAACATTTCATGTAAATGGAATCATTCAATAGGTGACCACTACCTTCT
CTCTGATTTTCACAATGCCACCCTCTCCTGGTTTTACTCCTGTCCCTATCAGGCTTTTTCTGAGTCACCT
TTTCTATCAGGTCCTAAGTGCCATGATTCTTACTTCAGCATAGCTGATTTCATTTGCACCTAAAGGTGAT
GACTTCTCTTTCTCTCTAGCCTAGAGCCCTTTTCTAAGCTCCAGACTCACATTATCAACTACACCTCTGC
AGGGCATGTCTACGGGCACCTCAATCTCAGCGTCTCTAGAACTGAGCTCAGTACCCACCACCCCAAGCCT
GTTGGGCCTGGGCTTCACATCTCAGGGAAAGGCACCAGATCCTCTGTCCCCCAACCCAGAAACTAGGGTA
GCCACCATCCTTCACTCCTCTCGTTTCCACACCCAGTAAATTACTCCAAAATCATCTCCTCAATACCATA
AAATTTATTTTCTGAAAAAATTTTACTCCTTAGAAATTCTTCAAATAATGAGACACTATCAACTTGTTTT
GAACCAAAAAGCACTTTTTAGAGAAAACACATTACCCTGAAATGACCTCAGTCAGGCCAGTTTTGGATGC
TTATAAGTAGTCCCCTGACAAAAATCAGTAAACAAGGAGACAAAGAAATTTAACACAGACTTAGTAATTT
TCACAATCCCAAGAATTCCATTCAGACAAGCCTCTTAGAAATCACTAAATAGCAAAGACTTTTTTAGATT
TTATAATTGTACTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTATACACACACAATTTTTTTTT
TTTTTTTTTGAGACGGAGTCTAGCTCTGTCACCCAGGCTGGAGTGCAGTGGCGAAATCCTGGCTCACTGC
AACCTCTGCCGCCTGGGTTCAAACCATTCTCCTGTCTCAGCCTCCTGCCACCACGCCCAGCTAATTTTTG
TATTTTTCGTAGAGATGGGGTTTCACCATGTTGGCCAGGCTGGTCTCGAACTCCTGACCTCATGATCTTC
CCGCCTCAGCCTCCCAAAGTGCTGGGATTACAGGCGTGAGCCACCGTGTCTGGCCCACACAAATGTTTTT
AAAGGAGTCTTTTAGGCCAGGAGCAGTTAGCTCATGCCTGTAATCCCAGCAGTTTGGGAGACCAAGGCAG
AAAGATCACTTGAGCCTCGGAGCCCAAGGCTGCAGTGAGCTATGACTGTAACTGCATTCCAGCTTAGGTG
ACAGTGAGATTCTATCTATACACACACACCACACAGTCTTTTAGAAAAATTGAGATAGTAATGGATAA
TAAGAGTTGAGGTTTGGGTCAAAATAATATGGGAGGGGTTAGTGGGTAGAATTTGGCATGAAACAAAAGT
GGCCACCAATTCATTATTGAAGCTAGATGATGGGTATGTCGGCATTCACTATACTATACACGTAGACACA
TTTGAGATTTTTCTTTTTTTTTAATTTTATTATTATTATACTTTAAGTTTTAGGGTACATGTGCACAATG
TGCAGGTTAGTTACATATGTATACATGTGCCATGCTGGTGTGCTGCACCCATTAACTCGTCATTTAGCAT
TAGGTATATCTCCTAAAGCTATCCCTCCCCCCTCCCCCCACCCCACAACAGTCCCCAGAGTGTGATGTTC
CCCTTCCTGTGTCCATGTGTTCTCATTGTTCAATTCCCACCTATGAGTGAGAATATGCGGTGTTTGGTTT
TTTGTTCTTGCGATAGTTTACTGAGAATGATGATTTCCAGTTTCATCCATGTCCCTACAAAGGACATGAA
CTCATCATTTTTTATGGCTGCATAGTATTCCATGGTGTATATGTGCCACATTTTCTTAATCCAGTCTATC
ATTGTTGGACATTTGGCTTGGTTCCAAGTCTTTGCTATTGTGAATAGTGCCACAATAAACAAACGTGTGC
ATGTGTCTTTATAGCAGCATGATTTATAGTCCTTTGGGTATATACCCAGTAATGGGATGGCTGGGTCAAA
TGGTATTTCTAGCTCTAGATCCCTGAGGAATCACCACACTGACTTCCACAATGGTTGAACTAGTTTACAG
TCCCACCAACAGTGTAAAAGTGTTCCTATTTCTCCACATCCTCTCCAGCACCTGTTGTTTCCTGACTTTT
TAATGATTGCCATTCTAACTGGTGTGAGATGGTATCTCATTGTGGTTTTGATTTACATTTCTCCGATGGT
CAGTGATGGTGAGCATTTTTTCATGTGTTTTTTGGCTGCATAAATGTCTTCTTTTGAGAAGTGTCTGTTC
ATGTCCTTTGCCCACTTTTTGATGGGGTTGTTTGTTTTTTTCTTGTAAATTTGTTTAAGTGCTTTGTAGA
TTCTGGATATTAGCCCTTTGTCAGATGAGTAGGTTGTGAAAATTGTCTCCCATTTTGTAGGTTGCCTGTT
CACTCTGATGGTAGTTTCTTTTGCTGTGCAGAAGCTCTTTAGTTTAATTAGATCCCATTTGTCAGTTGTG
GCTTTTGTTGCCATTGCTTTTGGTGTTTTAGACATGAAGTCCTGCCCATGCCTATGTCCTGAATGGTAAT
GCCTAGGACCTCTTCAAGGAGAACTACAAACCACTGCTCAATGAAATAAAAGAGGATACAAACAAATGGA
AGAACATTCCATGCTCATGGGTAGGAAGAATCAATATCATGAAAATGGCCATACTGCCCAAGGTAATTTA
TAGATTCAACGCCATCCCCATCAAGCTACCAATGACTTTCTTCACAGAATTGGAAAAAACTACTTTAAAG
TTCATATGGAACCAAAAAAGAGCCCGCATCGCCAAGTCAATCCTAAGCCAAAAGAACAAAGCTGGATGCA
TCACGCTACCTGACTTCAAACTATACTACAAGGCTACAGTAACCAAAACAGCATGGTACTGGTACCAAAA
CAGAGATGTAGATCAATGGAACAGAACAGAGCCCTCAGAAATAACGCCGCATATCTACAACTATCTGATC
TTTGACAAACCTGAGAAAAACAAGCAATGGGGAAAGGATTCCCTATTTAATAAATGGTGCTGGGAAAACT
GGCTAGCCATATGTAGAAAGCTGAAACTGGATCCCTTCCTTACACCTTATACAAAAATTAATTCAAGATG
GATTAAAGACTTAAACGTTAGACCTAAAACCATTCTTTTTCTTTTTTTGAGATGGAGTCTTGCTCTGTTG

FIGURE 1 (continued)

CCCAGGCTGGAGTGCAGTGGTACAACCTCGGCTCACTGCAACCTCTGCCTCCCAGGTTTAAACAATTCTC
CTGCCTTAGCCTCCTGAGTAGCTGGGATTACAGGCATGTGCCACTTGTAATGCTAATTTTTTTGTAGTTT
TAGTAGAGACCGGGTTTCGCCATGTTGGCCAGGCTGGTCTCGAACTCCTGACCTCAGGTGATCTGCCCAC
CTCAGCTTCCCAAAGTGCTGGGATTACAGGTGTGAGCCGCTGCACCCGGCCCAGCCACCGTACCTGGCCA
AGATTTTTCTTTAAAAATGTCTTTTTTATTTAGACACAGGGTCTCACCTCTGTTGCCCAGGCTGGAGTAC
ACTGGTGTGATCATAGCTCACTATAGCCTTGAACTCCTGGGCTCAAACAATCCTCCGACTTCAACTTCCT
GAAGAGCTGAGACTACAGGTGCATGCTACCATGCCTGGCTAATTTTTTTATTTTTATATTTTTAGAGACA
AGGCCTCACTATGTTGCCCAGGCTGGTCTCCAACTCTTGGGGTCAAGCAATCTTCCTGTCTCAGCCTCCC
CAGATACTGATATTATAGGTGTGAGCTACCATGCCCAGCAGAGATTTTTCATAACATGTTTAAAGCAATA
CAGTAACTGGTTATTTTGAAGATTATTAGTATATATCCATAGAGGAATTGAGGGGGGAAAAGCAACATCT
TAATGTTATACTAAAAGGTAATTATGCTTAGGTTACAATTTTCAGTGATAACATCACATACTAATTCAGA
AAGTATTCCCTTTGCAGCAACATGGATGAATCTAAATAACATTATGCTGAACGCAGACACAAGAGTACAT
ACTGTATGATTCCATTTATGTGAAATTCCAGAATAGGCAACACTAATCCGTAGTGACAGAAAGTCAATCA
GTGGTTGCTGGATGGGGACAGAGGAGACTGACTGCGAAGGCGCACCAGGAAACATTTTGGGGTGGTGGAA
ATATTCTCTATCTTGATTGGGTGGAGGTTACATGAGGGTATACATTTGTCAAAGCACAAATTTTACACTT
AAAAATGGATGTATTTTATATGTAAATTATTCCTCAACAAAAATTATTTTTTAAGTAAAAAAAAAATCTA
AGTAAAAAAAGTTGGCCGGGCACGGTGGCTCACACCTGTAATCCCAGCACTCTGGGAGGCCAAGGTGGGT
GGATCACCTGAGGTCAGGAGTTCAAGACCACCCTGGCCACGGTGAAACCCCATCTCTACTAAAAATATAA
AAAATTAGCTGGGCGTGGTGGTGCGGGCCTGTAATCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATCGC
TTCAACCCGGGAGGCGGAGGCTGCAGTAAGCCGAGATCACACCATTGCACTCCAGCCTGGGCAACAAGAG
CGAAACTCCGTCTCAAAAAAAAAAAAAAAGTTGTTTGCTCTCTCTCTCAACTTAGAAGGGAGGGAAAGTGA
TGATATGCTTTGAGAGATTCTATTAGATGACTCAAAAAGCGACTCATGGTGAAAATACAGAAATCCAAGA
TTCATGTGAAGAGTTGAATATAGTTTACTGAAAATGTGAGTGTGGGGAAAATCAATGTTCGTGAATCAAT
ATATTGTTTTAAATATGTGATTTAAAGTATGTACCTGTAGCTAAATAAACTATTATATGTGGACATTTGC
ATCTCTAAAAAGTTTATATTTTAGTTGCAAAAAAAAAACAACCCACAAAACAACTTGGAGTGACCCTATG
ATGAAAATGAGTGTTTGCCTTGTATCTGGAGTGGCCATCTCTTTCAGGCATATACAGTCTCTCACTTTGC
TCTATCTCCACAGACACTAACAGGTTTCAGTAAAGCCAAGTGTCCCTTCTCAGTGCTCCAATGGCCCCCA
TCACACTGAATTGTCATGGTCTGTTGGCATTTCTGTACCCACTGCTGGAGTGGGAACTTGTTCTGACTCA
GCTGTGCTGTCTTAGTGCTCTAGAGGATGCATCCGTGAAGCGTGTTGCAAGGAGGAGAGAGAAAAACAGA
AAAGTGCAGGTCTGCCCTGGCCTGGGCTTTCCCCTTCTCTTCCTTTATTGCCATATGTTGCCTCAGTGAT
GCAGTCACAGTGTCCCTGCCACCTTTCAGAAGAAGATACATCTGCAGCCCAGCTGGAGAACCTCAACATC
TGGGTCCCACTATGGGGGCCAATCAGCAGAGATACACCAAGGTCAATGGAGACAGCAGTCCCTGGGAGCA
GCCGAGCCAGGTGTGATTTTGCCTTGAGAGAGAACACGAGGCTCTTGAGGGACAGATAACACAACCCAGG
TGAGGAGGAAAGCAGGTGGACATGACCTAAGAAGTGTGAGGCCTGATGACTAAGTTGGAGCCACAGATAG
ATTTGGGGGCCAGGGGTCAGGAGCCTAAACAGCAGGTTGTGGGTGGAGTTCAAGGTGCACTGAGGTTAGT
TCTTAGCAAGTAGTACTGGCTGTGTGCTGAGGTGCAGGCTGGCTCACAAACCCAGAGGAGGGGCTGTTCA
GATGTCTAACACGAGAAACTGAGTAAAAATTAAAGAATGGTTTAGGCCAGGTGCAGTGGCTCACGCCTGT
AATCCCTGCACTTTGGGAGGCTGCAGTGGGTGGATCCCCTGAGGTCAGGAGTTCGAGACCAACCTGGCCA
TCATGATGAAACCCCCGTCTCTACTAAAAATACAAACAATTAGCTGGGCATGGTGGCACGCGCCTGTAAT
CCCAGCTACTCAGGAGGCTGAGGCAGGAGACTTGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAACCGAG
ATTGCGCCACTGCACTTCAGCCAGGACGACAAGAGTAAAAAAAAAAAAAAAAAAAAATGGTTTAAAGAAA
AAGGACAATGTTTTACACATGGATCAAATTAGACACTGCAAGACTATAAATCTGCACCCTTCTAATGTGA
AAAGGGCTTCACTGAGCTATACTTGTATATTATGCCCTCGATATTCACTCAAGGCCATTACAAGGAACAA
ATGAAAACGGCATCAGCATTTGCTATTAACCAGTTGAGAACATTCTCCACTATTTCAACTAAATAAGTAT
CCAGGTGAGAAACTTCTTTTATAATTTAACCCCAGAAATTTTTTTTACTCCAAAGAACCAGTTAACAGAA
TAGAAAGTGTTATTGTTTTGGCTATCAGGAAGCTCAGCCATGTTTAATTCTCAATCACATCAGCTACATT
AACCCATAAACCATATTATCGTCCTCCTCCTTATAATCTCATCTCCTATTTCTATATTTTATTCTCTATT
TTTAAGTACTCAAAACATTTTTAAAGGGCTGAAAAAGAATACACTTGTGGTAGACATAGCAACGTGCCAC
CCAGATCCCCTTCAAAGAAGGACTTGTTGACCCAACTATTGGGAGAGCTGTCAGCAGAAAATCTTCAGCT
GTCAGCCCCTCGAAGATCATCTTGGCTGCAGAGTGCCATCTGGCCCAGGCTAGGCTCTTCCCAGGACATT
ACAACTCCTTTCCAGGCTAGTGCCAGACAACAGAGATCCTGGGAGTTGGCTGAGACTGTCATCAGGCCTG

FIGURE 1 (continued)

CATCTCAGTTTAGTTTTCCCTGTGCCCACTCCTGTTTCTTTCCAGTACCTCCCAGAGTGTTGATCCCAGG
GCCACTCCCCAATAAACATACTGCACACTAACCTGTCACAGAGTCCACATCCAAAGAACCCAACCTGTGA
CAGCACCAAATCAAAAGAGACTCAGGAGGCTGAGGCAGGACTGCTTGAACTCGGGAGGCGGAGATTGCAG
TGAGCCAAGATTGTGCCATTGCACGCCAGCCTGGGCGACGAGAGAGAAACTCTGTCTCAAAAAAAAAAAA
AAAAAAAGAGAGAAAACATATCAGGTAGGGGTATTTTACAAAGGAGAGAGGATATACAATAAAGTGTTCA
TACATACATGGGAAGCAAAACAGCACTGACTCTGGGGCCAGACTACCTGGGTTTGAATCCTGCCTTTTAG
CTCTGTGCCTCAGTTTTTTCATCTGGAAAATGGGGATAATAAGAGCACTTATAGGGCTGTAATGAGGAAG
AAATGAGACAATGTGGATAAAGCAGTTCCATAGTGTTTACTATATGTCAACCACTGTTCTAAGTGGTCAT
TTAATAAACAGCTGTGAGGCCAAACCCACAGGTCCCGAGGGGCAGTTGGGCTGGGACTCTCCCCAGACTC
TGGGCATGGGCACAGGTACAGTGTAGGCCAGGGCATGCTGAAGCATGCATGTTCACAGAAATAGGCCTGA
GCAGGGCTAGCATGGGTGACGTCACAGGCGTGTGCTTGTGTGGGTGCTGGGCTGCTCCTCCCAGACAGCG
CAGCTGCACGTATTGCCATTCACACCCACGCACCCATATATATGCTGAGCTGGGGGAAGCCCACACAGAC
CACACCCTCTGCATGCCCTGTTTTTCCTGCACCTCCTTTGGTGGAAGGAGGCACCTGAGGCCTGGGATGC
TGGCCCAGAAGTCCCAGGAGGAAATGGGTCCTGTTCCCTGATTACAGGCCTGGCAACGGGCTGAAAACTC
AAGCTCTTGTTGGCAGGGATTTCTTGAGCCCCTAGAGGTCCAGACCCAGAGGCAAAAGTAAAAGCAAGGA
AGCCTTACCCTGCATGTTAGGAAGCTCCCAAAAAAATGGAGAAACGGATGTAAAAAGTGCATCAGAGCCC
ACAGGCTGCCGGAGTCAGCACAGTAAGCTCAATGAGGGCTGCAGCACTTAAGAGGGTGCCTCCTGTACAA
AACAGGATCAGACAGCCAGAGAGGGGCCCCATTCAGCCCCCGTCTGCCTTCCTGGTCTCATCACTCCCTG
TCCCCTCCTCAGTCAGGAAACTCTAGCTTTGTAACCCTAAATTCAACAACCTCTTCCTGGCCTCAGGGCC
TTTGTACATGCTGTTACCTCTACTTGGAATGTACTTTTCTCCAACCCACCTTTAATAATTCACCTCGCCA
TCGACTCACTTCCTTTAGACCTCTGCTGAGGTCTGAAGAGATCTCGACCCAATGTTTTTCCTTCTAGCCC
TCATCATAATTGTCTTTATGTAACAGAGTGTTTATTTAATGTCTGAACTCCCAGAGAGCTGGCGCTGTGT
CTCTCTTGTGCTCCTCATGTTGTCAATGCCCAACACAGAGAAGAGCAGGGTCCACAGAACTTCAAGCCTA
AGCCAGTTCAAGCCACACTCTGTGAGCACTCACGTTCTGCTGGATTCCCTGTGCCCAAGGCCAGCGGTGA
GCATGCCTCCCCTCACCCATGCTGATTAACCAGATAGCCTCCATGCCCACTGACTACTGACCACCAGGAC
TTACCTAAGCCAGTGGATCTCCTGTGAGGCAGAAAACTCATGGAGTCAGGCCGACTTGGGTTCTAGTTCC
CACCTAGTCATGTTATGTGGCTTTGGGGCAAATTGTAGAACTTCTCTGAATCTCTGTTTCCTCATCAGTA
AATTGTGGACCATCATTCCTGATTAGAAGATAATTATGAGGATCAGGTGTGACCACAGGTGCACACCTTC
AGCACAGGGTCTACGCTAGCTCCGTCCCGCCCACGTAAAGACCTGCCACTAGGTGGCAGTCCATCTCAGC
TACCCCACCGCTCCTTACTCCACAGAGGCTGGCTAGGACAAAGGGTCTCAATGTCATGCTGAATTCTGAG
CTTCTTAGGGGACGCACTTGAGGAAATCAACGTTAACACACAAGTTTCCACTACAGCAAGACAAAGTCAG
AAGCAGCAGCCCCAGGTCACTATCCAGCTGAGTGGGTTGCCTGAGCACACGCTCTTACAAACTCTAGTCT
AGTCCTACTATCTCACAATTCCCAGGAAGCCTGGCTCTTTCTCTGGCATCAGCTGGAAGCTCTGTTGGGC
TTCTCACCTCTGAAATGCAGTAAGTTGTCCTGCTGTGCCTGGCAGCCGACCCACTGCCTGGCTCAACATG
TCAGACAGGCTCCACCGCGACCGTGGGTGTCCTCAATTTTGGCGGTGCTGACAAGGGTAGATAGATTGCA
GGGGTGAGTTTCAAGAATGGCTTCAGAAAGACAAAGAGTATGAATTATATTCCATAACCAGAAAAAGGCC
TTGTGGCTGGAGAATGGAGAGTGAAGGATCACTTGTGAGAGATGAAACTGGTGAGATGGGCAGGTCATAT
AGAACCTGCTAGGCCAAGCAGGGAGTGTGGATTTTAGGTGCAATGGGAATTCACGGAGGGTTTTAGCCTG
GATGTAGGGGATCATGATTTAATTTCATTTTAAAGATTTAAAGCATGATAAATCCAGGCAAAACCAAACT
GATAGATCCAGGCAAAACCAAACAAGGTGAGTAGTCTGGGTGACAGGAGATGGGGCCTTCAGCTTGTGGG
CTGAGTGACAAGGTCTTGATGGATTGGAGGTGAGGCAAAGGGAGGAATCAAAGTTAGCTGCAAGGTTTTT
GACCTTCCAACTTAGAGAAGTTTAGCGCCGCGTTCTGAGAAAGTGAAGACTGTGGAAGGAATCGTTTGGG
GAGGGAAGGCGAGCTGTCTAAGGGGGGGGGATGTGGAACATGCAGTGGGATGCTGGGGCCTGGAACGTAG
GGGAGATGCAGGTTTGGAGTCACCGGTGCCTGTGTTGTTGGGCAAAGCCAGGGGAAAGGTCAGGTCGCCT
TGGGATCTGGCCTAGCACTGAGTGCAGAGGAAGAGAAGCTTCTGAGATCGAGAGGCAGCGGCTACAGGAG
GAGGAAGAAAGCAAGGCGGGGAAAACCAAAGTTCAGGAGAGCATTTGCAGGAGGGCGCTGCGGGGTAGGG
TCTGAGTCGGAGCCCCGAATCGGACTCGAGTCCTGTCGCGTGGGGACGGAGCGTGCAGAGGCCCATGCGA
GGGACAGACACAAAGGCCCTGGGAGCTGCAGGTCAGACCACTGGACAGCGCGGCCGCGGACCTAACGCCC
CTGTAAGGGGTGCTCACGCTTGGGGGGAACTCTCCGAAAGAGAGGACCACTGAAAGCCACCCTGGCAGCA
GGGGCGGAACAGACAGACGTGGGTCTGGCCGTCGCCAGAACTGCCTGCGGACCAGCCCCGCGCTGCCGGG
GGGGCGGGACATGTCGGCTGTCCATCAGTGCCCGCGACCAATCCGCAGGCAGCCCCGCCCCCGCCCCTCC

FIGURE 1 (continued)

CGGGAGAGGGCGCGCGGAGGACCCGCCGCCGCCGGTGTGAGGCGGCCCGTCCTGGCTCCCTTGTCCGGGA
AGCCCGCCCAGGTAACTGAGTTTGGCCGGGCATTCCCGGAGGACGCGCCATCCCCTCACGTCCCGTCCCG
GTCGCTGCATGGGCGGTGTTCGGGACGCGGGGGCTGCGTCTGTGCGGGACCGCGGGGTAGCGGCCGCCCG
TGCGAGTACGCCTGACTGACGCGCCGGCCGCCGGGCCTGCGGCCTGTGGGCGGGGCTGCCGTGCGTGACA
GGGCCGCTCGTGGCCGCCGGGCTGTGTCCGGGGCCGCGTGAGAAAGCTCTGCGGGACTGAGGGCTGGGTG
GGTCGACCGGGAACGGCGCGCGCTCCCGCCGCCATCGCGCCTCCGTCCCCGCCTGCGGCCTGTCTGGGGG
TCGCGGGGCGCAGGCGCGGCGGGCCGACGGGCGGGGGTCCTCCCCACGGGTGCGCGGGCGCCTTTGTTCC
CGGCGCCGAAGCGGGGTGGGGCCTCAGGGCAGCCCCGCCCCGCCGCGCTGAGGCCCCGCCCCGTGTCCGC
CTGCAGGAGCCGCCGCCGGGTCCCGCTCGTCTGCCGCCTCAGCCTCAGCCCCAACCTCAGCCGCCGCCGT
TGCGCTTGCTCCCGGGCGGTCCTGGCCTGTGCCGCCGCCGCCCCCAGCGTCGGAGCCATGGCGGGCGCCG
CGTCCCCTTGCGCCAACGGCTGCGGGCCCGGCGCGCCCTCGGACGCCGAGGTGCTGCACCTCTGCCGCAG
CCTCGAGGTGGGCACCGTCATGACTTTGTTCTACTCCAAGAAGTCGCAGCGACCCGAGCGGAAGACCTTC
CAGGTCAAGCTGGAGACGCGCCAGATCACGTGGAGCCGGGGCGCCGACAAGATCGAGGGGGCCAGTAAGT
GCGCCCACTTCCTGCCTGGGCCCGCCCCGCGCGGGGGTCGTGGGAGCCCGGCCCGACTGCTTGCACCCCG
GCCGGCCGCCCCAGCGACTTGGGCAAACTTTCGGGCCCTCCCAGACTCCCTCCGGGCCCCGCCCCCGCTT
CGTCTCGGGTGGTCACTGGGGGCGGGGGGCATCCGGGTCCTCGGTCACCTGACAGGACACCCCCCCTCCC
CCAGCTGGGGGGAGTGTTCCAGGCGCTTTGCCCTGAGGCCTAAAAATCCTCGCGGGCTGGAGACCTGCGG
TGCAGGCATCGGGCCCCCCAGACCCTGGGAGTGGTGGCGGCGTCGGCGAGGGGAGCTAAGGCAGTGGCCC
CCACCCTGCACGGGAACCTGGGGCCTGACCAGACGGTCCCCGCCCACTCTTTATCCAGAAAGAGCAGTCT
GTGAAACTCTCCGGGCCCCCAGGCTGGGCTCTTATTTGCAAAGGAATCTTTGGGTTCCCTAAGTAGAACT
TAGGCAGATGTTGGGTAGGGCTGGTCTTGGAGCAGAGCTGGGCCTACTCATCTCCCTCTGGGGGAGAGGG
AGGAAGGTGGTCTTGTTTGGTTTGGAGAAGCCTGAGAGAAGCCAGTGGCTGGAATTTTTTTTTTTTTTT
TCTGCTACTTTTGTCCCAAAGCTGGGTTTTGGAGGCCTATGTGGGTGGGCAGACACTCAATGCCAGGGCA
GGGACTCCCCTTGCCCTGGGAAGCACGTTCCCAGGAGATGGGCCCCATAAAGGCCTGCCCCAGCGCCTTG
GAGTCAGGTATTCTTCTCAGGAGTGCAGCTAGTTTGTGAGTCTAGCCCTTTGTCCTCTGTCCGGTGGCTT
CAGGGAGCGGGAGCGGCTTCTCTTAGTTTCCTGCCTTTTCGCCTTCCCAGGCCTGAGCTTGGCTGCTTTT
GCGCTGGTCTCTAGTGGGAGGAGGGAGTTGGGGGATTTTGAAAAACCCCAGATCTTTGAGAGTTGTTCCA
CTTAGCGCGTGCCTGTGCTGTGGTCGGATGGGCACTCTGCTCTGCCCTCCATTCCCCCGCCTCTCAGTGT
GAAGAGATGGTGTGTCTGCAACTCTAGACTGGGTTGCTTCTTGCAGGGACCCCCGGAGACTAGGGTTAGA
GAGACCCAGGCTCAGAACCAGGTCTGTGTGAAGGAGGGAGATCAGGAAGTGACACCCCAAGGGGGGGTCC
CACAAACCTTCTTGGGTATGGTGTGCATGTGTGTAGATAGTTGAGGAGATTGGGAGGAAGGAAGGTCTTG
TGGTGAGGCAGCCAACCATCCTCAGCTACAAACTCCAGATCTGACACAGATCTAATGCAGCTGCTCAACT
TAGAAATGGCAGCCCCCTTCCTCAGTGCCCCCACTGACCCTGTCAGCCATTGGGAGAACATTTTAGTGAC
TTGAGAGCCTGTGGATTCCAAAGTAAAGGAAGAATCGACACTGCAAAGAGCTGAGATAACCCTGGGAACA
TCACTCAGGCATCAGGCTCCAGGCATGGTCCCCTTCCTTACTCCCTATGCTGTGTTGAGTTGGTGGCACT
GGCTGGAAGTTCTCAGAGATCTCCTGGGTAACAGACTGCATTTTAAACCACGCATATTAGCAGGCAATAA
ATGTAGCACAGTGGTTGATGGCAAGTCTGGATTTGAAGCCCATATATTCATTGTGTGTTTCCCGGCCAGT
TACTTACCTTCTCTGAGCCTTGATTTCCTCATGTGTAAAATGGGGGTAATAATATATCCAGTATATATGG
TTGCTCCAGGATCAAATGAGACAATTCATATAAAACATCTAGCATTGTCTGACACATAAATGTTTAATAA
ATATGAGCTGTTATTAGCAATAACATTAACAATAGACCGTGGCTGCCCTTCAAGACCCTGAACTGGGAAT
GGTGAGGGGGTGAGGTGTGGCTATAGGTGAGGATGAAGGTGCAGGAAGGGAGGAGGACGGTGACCAAATT
CACATTTCACTTAGATTGCTACTCAGAAAAAGGCAGGAAACAGTTTTGTTTTGCCCCAACCCATGTGCCC
ACTCACCCACCCACCATGTAGAACAGTGTTTCTGTAGAGAAAGTGTTTGCAGTTGTGCACATTTGACTCC
TGGGTGTGACCTTTCTTGTTTGTAAGTTGGGGCCTGAACAGAAAAGAGGGGTGCAGAGAGGGGATGATTT
ATCATGCCTCATGTATTTGGGGGATGGAGGCAGGCATACAGAGGACCTGATAACCCCCTACCCAGGGGTG
AGCAGGTGGGTCAGCCAGAGGTGTACAAATTCAGTGATCTCATCAGTTAGCTGGGATTTAACAGGCCTGG
AGAGTAGGCAGAGGATGTAGGAGGACCCTGGCTTTTGGATTTTGGGGGCTCAGATTGAAAAGAGCCTGGA
TGAAAAGTCTGGTCGATGCTTGTGTGTTCAGACTTAACTAATGGAGGCTTCCACTGAAGCCGTGCCCTGC
TTCTACCCATTCGTGGGCTCTCCTTGTTGGTGGGTTCTGATCCCTGCGGCCTCTGAGGAGGTTGGACTGC
CAGCCGGGTTTTCTGCCACCTGGACTCTTGCCCAAGCACCTCAGGTATCTGGCCTTTCCTGCTGACCCTA
CCAGGGTACCAGCAGTGCCTGAAGCCTGGCCTAAGAGAGAGACACTGTGCTACCTTCAGGGTGTTGGTAG

FIGURE 1 (continued)

ACCTGAGGGAGAGACAGTGTGGTTTAAGGAGCACTCATACTGATATGTAAGACCTTCTTCTGCCCTGACT
CTGTGCCCTCTCTTGTCAGCAGTTGTGAAATGGAGCTGACACCTCCTGATTTCTAGGGTGGTCATTTGGC
TCAAAAGCGGGGTGGGGAAGTGCTTAGGTGTTGACAAGTTTGGTTGTCCTGGTGGTATGACAGGAACCAG
GTTGGTGTTTGGCCTTTTATGTTGCAGATACTGACATAAATGAATAAAATGCAGTTATGTAGAGTTCCAG
CTGAGTGCTATTGAGACCTTTCGTCCCATTTTACAGATGAGCAAATGGAAATGGAGAATCGTTTGTGCCC
AAGGTGTTGTGTCAGTGTGTGCCAGGGCCTCAGCTGGGGCCAGCTCACTAGTCAGAGGCTGACTAGCAAC
CCCAAGCCCATGTTCCCTGTGGTCCACGTGGCTCCTCTGTGAGACACCTTTGTGCTCAGACCATGCATTA
CAGGGCAAAGACCACTTTGGCTTTTGTATCCCAAGACAGCCTCAGCCTCTCTAGGCTCTGGCTCCACACT
TTTTCTTCTGGTGTTTTCTGAGTTGAGATGGTTCAGACTCGTGTTTAATGAGGTTGTCCATTTGAGGGTC
TTTGTGGGCCCAGTAAACACTGGTGTAGACACTGTGGAGGTACTCTGAATACTGGCTGAGCATGTCCATG
GGGACTTCTGAGGCCCCAGGCTTCTGTCTTTGGCTGATCCTTCACTAGATACTTTTCTAGATGCCAGGCC
CTCTGAGGTGAAGGAGTATGGGTGCTTGCTTTTAGGGAAATGAAAACAGGCAATGACAATTGTGAGCAGT
ACCTTTGATGAAGAGGGTGAGGGTGGCGGAAGAAAACAGCTAACTGCCTTGATGAGGCAGGCGGGCTCAG
AAGGGAGGTAGTAGTGGAACCAGCTGGCTGGGGCTTGACCCCTGTGGCTGGGGAGCAGACCACACCAGGA
GGCCTGCTCCGAGGGCTAGGCCCACAGCACGGGAGAGGGCAAGGCCCAGGCCGGTGTCATCAAGGGTTTT
CTTTGTACTGGCTGTTACTCCCAGTGGGAGAGGGGCAGGAGCACATGTCCGGATCTCCAGAGCTAGCCAT
CCCTGCCTGTGTATTTCCTGTCTGATGTAGTTTTTTCCAAGGGAAGTCAGACCTTTTAGTGTTTCCTCAG
CACCCCAGGCTTGCCCCGATGTGTGGGTTTCCAGGCCCCCCCGCCCAGCTGGGATCCTCTGTTTCCTGTG
AACCTAGGAAAAGGGCCTGCTTCACAGATAACTGGAGGAGCTGAGCACACCCAGTCCTGGGACCCACAAC
ACCTCCAGCTTCTCTCCAGACTCTTGTGTGTGTGTGTACACAGATGCACAGGATTCAGTTGGAGTTTAGA
GATCTTGGCTACCAGCTTTGCTCTGGGTAGCTTCTTGGAATGAGGCACATTTATTAATATTTGCAATAAG
TATTATTATACCTCCCCATTTGCCCAGTGCTAGGCACCAAGGATTCAAAAGTTTATTGAGACATGGTTTG
TGCCATTGATGAACTCTTGGAAAAGACAGATGTAGAGGCATATGATTATAACCCTGTGTGTTACATACCA
TAATATAAAGGCCTCTACCAAGAACTGTGAGGAGCTCTGCCAGGAAGGCATTAAAGGAGAGGTGACCTTT
GAGGTAGGCCTTGAATTACTGAGGCACCTGTCTGTGCCGAGGCTAAGGAACTGGGAATCACTCTGTGCAG
GGGTAGGGAACAGATATGGTGTGGTAGAGAGGAAGCTGGGACTGGTTGGAGACAGCTATAGCCCTAGTGT
GCCATGTCCAGCAGATTACACTCAGTCCTGGAGGCGACGGGAGTCAGCGGAGGCTGTTGTGGGACTGACT
TGCCTCTGCCTGGGAGACCACAGTGGCAGTGGTTTGTCAGGCAGGTGTTGGGGAGGGAGGCCAGTGAGCT
CCTACGGTTTGCACAGTTTGCAGGAGAGAGCTGCTGAGGGCCCAGACAAGACCTTCTTGCTGAGGCAGGG
TGGGGATGCCATGGTGGTAGATGGGAGAAGGGCTGGGTCTTGAGGGGTGAGACAGAGCTTAGTAGTTAAG
CATTTGGGCCCTAGACTCTGCTTGAATTAAAATCCTGTTGTGCAGCTTACTTGCTCTGTGACCTTAAAGC
ATATGACTACCTCTCTGGGCTGCTTATCTGTAAAAAGGATAGTATTAAATGGCATTTATTTTATAAGGTT
TTTGTGAGGATTTGATGAGAACCTGTATAAAGTGCTTAGCACCTGTATAAAGTGCTTAGCATGGAGTGTG
GCACAGTGTAAGTGCTTACTACGTAGGATCCCTGACAGGACAGAGATGAGGATTAAGTTCTCAGGAGGAC
CTGGTGGGGAGGAGTTCGAATGCACCTGCTGTCCTAAGGGGCTGGTGCCTGGCCACCAAGCCCTTTGATT
CAGAGGCAAGGAGGCCCGCCCATCCTCTCTTGCAGCTCTCAGCAGTCCCTCTATTGTCAGGGCTCTTTCC
CACTGCTGGTTTTGCAGGGAGACAGGGCAGTTGGCTGGAAGCAGCTGCTTTGGGTGGTAACCCCTTCTGT
AGAGTGAAGGTATGATATTGTCCTATTTCTAAGTGCCTAGCCCAGGACGCTATCTGGAGAGATCTTGTCT
TTGAGGAAGTGCTCTAATGCCACAGCCTCGATGTGGTAGGGCCTGCCTCTGCTGTCACTGTTCTGTGTCA
GTCTCCGTTAACTCACAGCATCTCTTCTTACTCTGTGCCTTTTCCTGTGGGATGTGGCTTCAAGGAGACC
ACAGATGATAAGTTGGAGGAAGGGAGTGAGGCCTGAGATTGCAAAGGTGTGATATTAGGAGACTGATTTT
TCCCCCTTTCCACTTGCTTTGTTAGAACTAGAGAAGTCACTGCAGACTGTGAGGAGAGTCCTAGGAGAGA
TGGGTGTGGGATAGGAGGATGGGAATGTTCTGGTGCCCCTTGTAGAGTGCCTTGTTGAGAGGAGCATGGG
AACAGTGCGTCCTTGGAGGGAATCTCTGAGAGCAGCATGTTTACAGGTGGCAAGACTCAAGGTGGAGCCA
CGGGTGAGGAGTGGCTTCAGGCTACCATTGACCAGATAGTCCCACCTTGCTGGTAATTGAGCTGAAGTGC
CTGGAGATTTGTGGCTAGAGCTGGTCAGATTTGGGTTCAGGTCTCAGCTCTTACTGTGACCTTGGGCAGA
TTACTTTTCCCTGTCTGAAATTGATCTTTAGCTGTAAAAGTAATTTCTCCTCACAGAGCTGTATATTAAT
AATAAGGGAGATTATATATAAGAGTAAGAGATTTTATGTGAAAACTACCCAGCACAACATTTGTCACTTA
GTGGCCACTTAACAGTATTCATTTCCTTTACTCTCACCTTTGTTAACCACAGAGCTCCAATCTTTTCCAC
CACTAAGCTCGGCCACAAGTGGCTGCTCCAACAACCTGGGCTAGGAGTCTGTTTCCTACTTGCTTTCTGT
GTTCCTTCCCTGAGTCTGTACACAGAGGACTGGGGCATCAAAAAACTCTGGAATTGGAATAGCATATTGG

FIGURE 1 (continued)

GAGTTCATGGAACATTTTCTCACCTGTTGTATTGTTTGAACTTCACAGCAGCTCCATGAATCCATGGAGG
GCAGGAGTTACTATCCCTCTCTTACAGAGGAGAAAACCAAGCCCTAAGGGTAAGGTCACATAGCAAGTTC
ATGGCAGATCCTAGGATTTCAGATTCCTGCTATAGTATTCAGTTTATTCTCCCATTCTGGGGAAAATGAT
AATAGGATGGACCGTTCTATAGGAACAGAGGGTTATTTTGTTTTGTTTTGTTTTTCTTCCCTCTGGCCAC
ATGTGTTTGACCAGCCTAGACTTCCATCTGTGGACAAGCTGGACTCATTGCCTCAATTTCAAAACCCGTC
CTGCACTCATCCTTGCCACAACACCGGTGTCGAGATGCTTGGCCCACCCAGACCTTTCCCACACTCCTAC
ATGGGGGTGAATGTAGCCGCTGATTGGGGGTGGGACACAGAAGAGCCTCACCCTCTTGACTTTCTGGTTT
GTGGTGACACTTCCGCCTAAGCTTCTACAGAACATGGGAACCTGGGGCTCCATGCCCCAAATATCCTGAG
AAGGGCTTTTCCAGGATTCTCTATGACAACTCAAGAGCATGCATTCATTCATGTGCTCTTTAATTTGTCA
TACATTTGTTGTGGGCCTTGCTACTGTGTGTTGGGCACACTGAGCTGGATGTGATTACTCCAGCCTCTGA
CTTGTTCATGGTGGCAGTAGATCTCTAGCGTGGTTTGTGTTCCATCTCACCATACCTACTCTCCTTAAAA
AAAAACAAAAAACTAGCTTTCTTGGGCCTCAGTGGCTCATTGAATAAGTGAGAGACGACTTGTGCTTCCC
TGGCTTTAGACTCTGGCATTTGCTAACTGTGCCAAGCACTGTGGAGACCAGTAGTGGACATAAGGTTAGG
GTAGATACAGCCAGAAAGGAGATAAATAGGCAGACAGATAAAATTCTTATAGGATTTGGTGAGTTCTATG
AAGGAAATAAGGCAAGAGGCTGCTCTGTCAGGGTAGGTGAGGGTGTGCTGTGATAACAAATGATGCCCAC
ATATCAATGGCTGGCAACAAGGAAGGTTAATTTCCCCTGTTTGCTATGTGTGCTAACCTACACCACCGTC
CCTGGAGAGTGGCCTCAGTGGTTCTGGGTGAGGCCTCTAGTACAGAACCTGAACACCCTGGGCAAACTAG
GCTGGAGAGGGATTTGGAGTATGGAGGTTTAGAAGGAATTAATTTCTATGACTTAGGATGCATGTGGTGA
GTGTGGCTTTGCTGTTGTGGTAGAGTAGAGTGCTGCCTGTGTGGGTCAAGAGACTGTCTTGGCTGACATC
TTTGAAATAGGTATATTTGTGTGGCCCTTGCCTAATTGTCATCTCTGCCATAGCTGCCCCCGCCTTCCCC
ACCAACCCATGGCCCTACTTGAGCTGCCTGCTGAGCCTACTCTGTTGTGGCCACAGTATCCTCCTGCTGC
CCAGAGTTTGAGTTTCTCGCTACTTCTGCCACTCATCACACTTGCTTCCCAGAGCTTTGCTGGGTGTGCT
GAAGTCTCCAGAGAAAGTGGGGAATATGGGTGCCTAGAGACTTCTAGGGGGTGTTTTCAGCCCCTAGAGA
GTAGAGAAGTGTGAGAAGGGGTTGGTCCCCGAATATTCTGTAGTTTTGGGGAAGAAGCAATGGGGACAGT
GGAGTTGGTTGCCTTAAGAGAGGCTATGGTCCCAAGAGATGGGACTTGGAGAGTCTCTACTTGCATTCCT
GGCTAAGCCCTTAATATTCTCGCACCCCTCCTTGCAAGACTAGTTCCTTTTGAGGTGGTTCTTGGCTAGC
TTTTGAGAGGCTGCAGTGGCTGTGTGCCCAGGCTTAAGTCCTAGCTTTCTCCCCACTCTTTACCTCCTAG
GAACCGGGCCCATCCTGGGGGAGGCAGGGAGGAGCTCCTTTTTATAGTCCACATGTAGGCTTTGTGTATA
GGCTCTGCTGCTTCCTTCCGGCCCTGGCCCTTCCTGGTGTTGGCCGGTGGCCCTGGCTTCAGCAAGACTC
AGGATGCAGAGTAAACGGGGCAGGGCGTTCTCCTACAGAAGACTGGCATCCCTTTTTACTGAGCCCAGGC
CTGGCACAGAGGAGGCTGGAGTTAGGAAGCAAGAAAACGAGGTGACCCAGTCCTTGATCCTGAGAAGCTT
GTGATCTGGACCATGCAGAAAACCGCTAATGCCCAGGGCTGGCAGGAGACAGCTGTGCCTAAAGTGCTGT
AGGCTGGGCCTGAGGGCCAAGATGGAATCGCTTTTCTCCCTGTAGCAGCCCATCCTACCCCCTGGGGTCC
CTCCACCTGCCAGCTGGCACACAGGTGTTGGGTAAAGCATCTGTACAAAGGCTGTGAGGGGCCTGGGCGC
AAGGCAGCAAGGCTTGGGTACGGAGGAGAGTGGGTGGTCTTACTGATGTTCTGGGCCCTGACAGTGAACA
GCTGGCCAAACTGGTGAGGAGTTGGGCCATGGCGAGTTTGGCCACTTGTTTGTGTGTGTTTAGTTCTTCC
TGGGCACAGGTGGGGAGTTCACTTTGGGGTTGGCTTCCTGTTTTCTTGGACACCTGGGGATATGGTTGAG
TTAAAATGTTCTGAGGGAAATGATTGTTGAGGGCATGGGCTTGGGTCATAGTGTCCTTGGCTTGGCCTTG
CCCATGGTAGGAGTCGGGTATTGACCACACTGGGTTCTGGCTGTGTAGGTGTGGATGTGTGGTGGGAGAA
TTCCAACCCCACCTTGACTTCAGCCTAAGGCCCAGAGAGTGTGGGCCTGAGTTCACAGGGTGACTAACCC
TAGGAAGGAGTGAAGGAGAGCTCCAGTTGGCCATAGGTCCCACAGGTTTCTCAGCTTACTTGGGGGCAGG
AGGTGAGCTAAGGAATACAACTCCATTCCCTCAGTTGGGAGGTTGGGCAGCGATGGGGGCAGGGGTGATG
GTCCTTCTCTGAGGCACTGAAGACCCACTTTATGGTCACCCTATTCTGCCTGATAGTCCACCACCTGTTT
GGAGGCAGCTCCCCTCTTCCTGCCCTAGTCACTTCCTCCACCTTCAACAGTAATTGAGTATAATGTGCCT
GTGTTAGCTTGTCCATCCTAACTGGGACTGTGGCCTTTTCTTGGGCGTTCTTAGCATATCTACCAAGGAG
GTTGGAAAAGGTAACATATGTCACTTTGTTAAGGATTTTGCTGAGGGCCTTTTGAGGCCAGCAGTGAAAC
ACAGAGCATTCCCTCCAGTGAGAACAGAATGTCTGTTGCCAGACTGATCACAAGAGGATGGCCTGGTTCT
GGCCTGAGAACTGGTCTACACCGGAAGCATGAAGCTCCATACAATCATGTGTGCTAGTAAAGTTTGGGCA
AGCAGCTGTCCTAAGCAGGTAAAACGATAGGTTATTCAACTTCAACTTCAGAGAAAGAAATCCAAGGTAG
CCATCTCTCTCAGTAGGGGAGGTGAGTTCAAAGAATTTAAGCTGGGCTGGGCACGGTGGCTCACGCCTGT
AATCCCAGCACTTTGGGAGGCCAAGGTAGGGGGATCACGAGGTCAGGAGTTCAAGACCAGCCTGGCTAAG

FIGURE 1 (continued)

ATGGTGAAATCCCATCTCTACTAAAAATACAAAAATTAACCAGGCGTGGTGTCAGGCGCCTGTAACCCAG
CTACTCAGGAAGCTGAGGCAGGATAATTGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGCCAAGATCGC
GCCATTGCACTCCAGCCTGGGTGACAGAGCAAGACTCTGTCTCTTTAAAAAAAAAAAAAAATTTAAGCTG
GGCTTTCTGGGCAGGCAGTGAGTGAATGAGATCCCTGGCACCTTGGAGTGAGATCAGAGTCTAGATCACT
CACTGGGGCCCTGTTTCCCAGGAAGCAAAAAGGGAACAGGAGAGTGGCTTGGCTTGGGCTGGCATGGCGC
AAAGGGAGTGCAGCCAGATGCTGTGGCGGCTGGGTCAAGTAGCTCTAAAACAGGAGAGCCTAGTGGGTTC
TGCTGAAGCAGGATGTCTCAGCAAGCAGGCCTCTGACCTGACGACTTCCGGTCATTATTTAGAACGTCTC
CAGCCCCACAGATTTACTCTGTTGGAGGCTTAAGGACTAAACCAACATTTACTGTCCAAGAGGTGGCAGT
AACACAGAAACCAAAGAGGCAGGAACCAAGGTTGGGGTGGTGAGATGTCATGGGGTTCAGGGAGTGGCAG
AGGGGAAGGCCTCTATTCTCCCTTTCCCACTTGTCTCCCTACCTCAGCCCCTGTTGCTCTGACGCTTCCC
CCACCACTATGAGTCCTAGGCCCCTGTTGTTTCCTTGTAGGAGGGAGACCCCAGATTTTTATTTCTTCTC
CCAACCCATTCCATTTCCTCTCCCTTGTGAGAGGGCTCTGCAGAGACAGGGCAGCAGAGAGAGACTTGGA
GATATGCTGGGCTGTGGTCAGGAGGGCCTCATTTATCTAGTGAGCAGGAACAGGTTATATAGCAGTGATG
CTTTCATAGTATTTTTCTTGAATAAGGTCCCCAAAACCTTATTAAGTTCCTGGTAGGCATGGAGCATTGA
AGATGGCAGACATGGTGCAGTCTCTCAAGGAGTTTACGCTCTAGTGGAGAAAACAATCAGACAGCCTTAA
AATACATGTATGGCTACTATAATAAATACTGTGAAGCAGGAGTGCACCACGAAACCTGGAGTCCTCTCCA
TCCTCCCCTTCTGTCTGTGCTGGCCCTGCTTGGCCACTTCCAACAAGGATTCTGAGGCATTACAGAGCAC
ACGTCTAGGGTACAGGCAGTCTTGGCTTTGAAGTATTGTTGGCTTTGCCACTCACCAACTGCCACCTTAG
GTAAGTTAATTAACCTCTTTGTGCTCAATTTCCTCACTCGGGAATTGGGGACCCTAATACTTACTTCATA
GTGTTATTTGCAAGTATAAAATATAAGGCAGTTTTTATCGTTGTAAGGCAGTCTTATCAAGAGCTTTATG
CAATGTCTATGCAAAGTAAATATGCAAGAAATTAGTGTTAGGATGCCAGATGCTGCTGTTGCTCATCGTC
TCTTCCCACCCAGCAGAGGTAGTAACTACTTCATCCTCTACTTCTCAGCTTCTTATAGTATTTGTCTGTG
GACTCTAACGTAAGCTATCTAGCATAATACTCATATCTAATTTTTCCTTCCACATTCAAGCTCCTTGAGG
TACTTGTATTCCAAGTATCTAGTTTAATGTCTCTCATGTAGGTGCTCAGAACGTATGGTTAATTTTGAAT
AATAAAGCCAGTGGGACTTCTCAGAGGGCTGGATTGGGGGCTGGTGAGAGAAAAGGAGATGCGAAGGATC
ATTCTGAAGTTTGGAGTTTGGGTACCTGTTTGAATGGTGATGCTCTTAGCTGACCCAGGGGGTATGGCAA
GAGGCCTTGGTTCTGGTGAGAGAGAGAAGACAGTGTTTGGTTTTGAGGAGTTGTCTTTGAGACGTTTTGA
GATGAAGAGTGGGGATAGCAAGTAGGCAGCTGAATTGAAGGATCTGAAGCTTAAGAGGAGAGGACTAGGC
TAGAGACCTGTTTGTGAATTATCTGTACATAGGAGGTAATTAAGGGTGTGGGCATGGCTGACACTGATGA
GGAAGAAGGCAGAGCACCGGAAGAGAGGACCTTGACCTGAGCCTTGACCAAGGCCATTGCTAAATGCAGG
TAGGCCTGTAGCGCACAAAGAAGCATGAAAACCAGGCAAGGTTGTGCAGGAGAAATCAAGGGCAGAGCTT
CAAGGAGAGAGGGCGTGATCAACCATGTTGATTGCTCTGAGGTGTCAGGAAGGAGGACCATAGATAAGTG
ATTTATGGGTCAGGCACGGTGATTCATGCCTGTAATCCCAGCTCTTTGGGAGGCCAAGACTGGCGAGTCA
TTTGAGCCCAGGAGTTCAAGAACAGCCTGGGCAACATGGCAAAACACCATCTCTGCAAAAAATATAATCA
GCCTGGCGTTGTGGTTTGCCTGTAGTCCCAGCTACCTGAAAGGCCAAGGTGGGAGGATCACCTGCACCTG
GGGAGGTAGAGGCTACAGTGAGCCCTGTTGGTGCCACTGCACTCCAGCCTGGACAACAGAGTGACTTATG
GGCCAGGCATGGTGGCTCACACCTGTAATCCCAGCACTTTGGGAGGCCGAAGTGAGAGGATCACTTGAGG
CCAGGAGTTTGAGACAAGCTTGGGCAACATAGTGAGACCCCATCTCTATAAAATATAAAGAAAAATTTTA
AAAGTGACTTATACCCATTGCTCTGGTTCTCCAAGTAGCCTGAGTGTACTATGTGGGGGAGCATTTTATG
AGGGACTTTTGAGGTCCTGGGCATCCCTGAGACATGGCCCTGGTGGGTCCCCAGTCTCTCTCCTGTAGCT
AGGAGCCTGGCATACACAGGCCATCTAGAAAGAACTTAGGCAGCATCAGTCTGCAAGGGAGGCAGAGTTT
GGAGCACACTAGACTCCTGACACAGAGGCTGACCCATGGCTGCCTGGAGAATCTTCTGGGCTTGTGCAGA
AAAGTTGGGGAAAGCCACCTTTCCCTACTGTGGCAGTCAAGGCTTGGTATAGGCCATCTTCCCTCCCTTC
TCATCCATGATACTCTGAATGCCCTGTTTGTGGAACTTAGTGGACTCCTGCACCTCTGTCTTGGTTTCCA
TGAACCCCTCTGCCCAATGTGTGCTTGTCAGCCCTCCAGACCTGGCTTTTACAGAGCACTCCAAGACATT
GCTCTACACACACTCAGCTCCACAGACACCTCCCTGTTGTTCTACTCGTTGCATGACCTCATAGTTATCT
GCTTCCCCATCTGTTTCCTCCATCAGGCAGGGGTTTTCTCAAAGGCAGGAACTCAAATGCCTTATTGATC
TCTGTTTCCCTAGGACCCAGCCCAGGGCCTGACATGGAGTAGATAGATGCCCGATAAATGTTTGATCAGA
TGATGGAATGAATGACTGCATAAGCCGAATAGATCACTGCTGAGTGCTCTTCCAGCTTTAATTTCTCTGG
GTGGGACCTCCTTTCCCTTCCTTCCTTTGGATTCTGTTCTTACCTCTGAAATAGGTGAGATTAATTTAGA
GTCCTAGGGAAGAGGGCTGCCTGCCTGGATGGTACAAAGGCTGGCTGTGGCTGCTCTGTGTTTCTCTGTA

FIGURE 1 (continued)

TACCCAGTGTCAGGGATAGCAGCTGCTGTGGGGACACTGCAGAGTGTCCCAGTTCTGCCATGACTCACCA
TATGACCATGACAAGACCCTTTGGACCCTCTGTTTCCTCATTGTTTCAAAGAGATTTGTCTAGAATCTAG
ACCAAGCTTGTCCAACTCGCTGCCCGCGGGTCTGGTTTGAAGGCAGCTGCTGCACAGTAATGGGAAGGAC
AGTAAGCCCCACCATCGCCTTCCCTTTGCCATATAACCCTGTGACCTCAGAAGTCCCTGAACCCAGATCC
TTGTTTGTAAAATGGAAAGGGATAGCTACCCACCCCTCCACTTTGACCTTCCTTTGGTGGCAGCCAGATG
TGCTCAGGGAAACCTCAGATTTGTGAGTATGTTTCTACTGAGAGGCAGGAGGAGGAATATTATAGTCTCA
GGAAGAGGGAGGAATGAGAGGGAGAGGAGAACTCTCACCCTTTCCACAGGCTTTGGGCATATGCAGCCAG
CTTGGAAATGCTGACCATCCTGTGACCTGGCTACTATTGCATCAGGCTTCCTTCCCACCTGTGTCCAGGT
CCTATCTTTGTCTCTTCTTTGGCTACCTCCATCCTTTTCCTTCAGAGCTGCAAAAACCTTGCCAAAGCCG
TATGGTCCTGATGGGTGCAGAGCCCCTGTGCCTCTGGCTGCCTGTGAAGGGGGATCTGCAGTGCAGTGCC
TGCCGTACCCCACAGGGAGTTGTATAGGAACCTGGGGATGGGGTGACTGAGGTAGGGGGCCAGAAGTGGC
CCAGATGATACTCACTTCTGCTGGAACTTTTCTTTGTCCATCTTTCAGCATCCTCTGGTGGAGAAGGCTT
AGCTCCATTAATGCTCTCCTAGGTCCTGGCTGTGTATTTTCTTTGGTATGGGAGTGGGGAACTGGGAGGG
ACTCATCTGTTTGCCACAGACTACATGTGGAGAGGGTGATTGGTGAGAGGTCATTTTGGAGATCTACACA
CCTCTTCTGACCCCTGGGACCACTCTCCTGAATCTCCTCATGGTCTTGGCTTCGGGCCCAGCAGGGCGTG
GGTGCTCGGCATCCTGCTGCTTTTACTGTTTTTCCCAAAGCTCTGTTAGCTTCCCGTGGTTCCCACTGGC
TATAGGAATCTTTATGTAAGGACTTCCCAGTGTTTCCAGACTGTATTTGCCCCCAGGGGTCACATTCCCC
CCAACTATGCCTGCTGCTGCTTTTTCTGTTCCCGTTGTTACCTCACTGACCACTGCATTTTCAGTATTTG
TTGTAGCCCCTCAGCCTCTGTGGCCCACTGTGCCACCTCTTCCAGGAAGCCATCCTTGATACCATCTTTC
TGGTACCATTTTTGAGCATCTGTGGCCTTTGCTGCCTGTTAGATAATTAGCTCTGGAATCTAACTCCCAT
GTGTTTACTCCTGCTCTTAAGTACTCTGAACATTTTGAGGCCTCCCCAGGCCCTGGGTTTGTGTTGGACT
GGTAGGGAATGGAGAGAAGAGTCAAATGTGGTTTCTTCCTTGGAGGAGCTCATAGGCCAGTGGCCTAAGA
CACCAGGGAAGCACCAGCAGGTGTGACAAGTGGTGACACACAAGAGAGGAGGGGGCACCTAGTGTGCCCC
TGGCCTGGGCCTGGTGGGGGCTTAAGTGAGGAGGTAGGAGTGGCTTGTGCAAAGGCTGAGGCAGGAAGGA
GTATGGGGAGACATGGGCTGGTGTCTGTGTTGTGTTAATTGGACTTGGACCCTTTTGAGGAGGGCTGGGC
TTTCCCTGCCTTCCTCCAGTGCCCTCTGCAGAGTGGGGCACACAGGCCTTGAGGGGTTCTGGGGTCCACA
GGCCACAGGTGGGGGTAGTAAAAACCCCCAGAAGGGAAGGAACCTGTCCAGGAAATCTTCGCTTACCTCT
TTCAAGCTCTTTAGATTTTAAAGAGACCTTTCATATTTACTATGAGTTGCAGTTTTTTTAAGTTACAAAA
TTTCTTTACTCCATGCATGTTTAAATGGATAGTTTTTGCTACCATTTACATCAATTAGCTTACACACTTT
GGGTTTTGTGTTTTTGTTTTGTGTTTTTAGAGAAAGGATCTCGCTTTGTTGGCCAGGCTGGAGTACAGTA
CTGTGATCATAGCTCATAGAGCTTCCTACTCATCTGCAGCCTCAAACCCTTGGGCTCAAGTGATCTTTCC
CACCGCCTCCCAAGTAGCTGGGACTACAGGCATGTGCTACCATGTCTAGCTAAGTTTTTTTAATTTTTAT
TTTTTGCAGAGGTGGGGTCTTCCTCTGTTACCCAGATGGGTCTTGAACTCCTGGCCTCAAGCAGTCCTCT
TGCCTCAGCCTTCTAAAGTGAGCGTATGCACTTTATAAAGGGAAAACCCTCTCTGAAGAGAAATATTTCA
GACAGGGCATGGTTGCTCATGCTTCTAATCCCAGCACTTTGGGAGGCCGAGGCAGGCGAATCACTGGAGG
TCAGGAGTTTGAGAGCAGCTGGCCAACATGGTGAAACCCCGTCTCTACTAAAAATACAAAAATCAGCTGG
GCATGGTGGTGTGCATCTGTAATCCCAGCTACTTGGGAGACTGAGGTATGAGAATCACTTGAACCCCGGA
GGCAGAGGTTGCAGTGAACCGAGATTGCACCACTGCACTCCAGCCTGGGCAACAGAGCGAGACACCCAGA
CCCAGAGAAATATTTCAGTGAAAGCATGTTTCATGTTCAGAAATTTGGGGTACTTTTGGTTATGGTTTTC
TTGGCCATATCTTCATCATTTGGTGGGTTTAGTTTTCAATATGTCCTCCTGTCCCTTTCTGATTAAATCA
CTTCTGTATCTCTTACCTCATTGGCATCTCACTGTAGTCCAATGAAGGAGGTGCCAGGAGTGGTGATTCT
ATTTTGCAGATGAAGAAAATGAGGCTCAGAGAGATGGGTCCAGGCCTCCTGCCCACCTTGCCAGTGCTTT
TGTTCATAATACCTCTCTACACCCTTTTTGCCTGCTGAGCGGTTAACAGGCTTATAAATTTGGGGGACCT
CTGTCTGTTGGGCTATTTGGAAGTGGCTTTTTTGAGCACAGGGGATACTAGGACACAGGTTCCAACAAGA
AACTTAGGTCTAATTTAGGGTCTTGGATTTGATGATTGGGCTCCCTCTCCCCCTTCTAGGGCCTGCCATG
TGTCTGCCCCCTAGGGCAGGATTGGCTGGCTCTCACTGGCTGTGCTCTGAGGAGCCCTGCCTTTGCTCTT
CTCTTTCTCTTCCCTAGGGTTCCTGCTGTCCTTGAACTCTGCCGGGGCAACAGGAATACTGCCCTTATGC
ACATCCTCGTGGTGGCCAGACAGGGTGGTTATCCCACTTTACTGGACAGGAAGAGAGCTAGTGGCAGGCC
TGTGACTTGGCCTGATGTCTCGGGGGAGTCGGGGTGGGAGCAAGAGTCAAAGACAGGAAGCAGCCCTACC
TTCAGAAGAGCCAGGCACACAGATGGGTCCTTTGTGGTTATTGTCTTCTCCCTTTCCCAGGTTCCAGACT
GGCTGCCCGCCATATAGCTTGTCCCTTCGACAGCACCCTCTCTCCCCACTCAGTGGATTGGGTGCTGTCC

FIGURE 1 (continued)

CAGGGTGGGGGCTTACTCTCCTGCAGAGGCAGGTTCTCAGCTGGCCCTGAGGGTTGTATAGCTTCACAGC
TCCCAGAGTGCTTGGGCATAGGGTGGCTCAGATGAGGAAACAGGCTCCTCTTTTAAAGGGAAAGCAACTG
CCATTACTGGCATGTCCAAAAGGGGGATGCTGTCCAGGACTGCATGGCCCAGAAGCTCCGCTCTGAGTAA
CTGCTGGTCTCTAATCTCTGTGGTCTCAGGCCAGGAGTCTGTCCCTGGGCTGAGAAGGGAGGGGAGAAGA
GGGAAGAGATGGAAAAGGAACATTGCTCTTCCCAGTCTCCCTGGCCTCGTCATATAACCTTTTATTTTAC
AAATTCAGTCTTGTGGCATTTTGCTTTAATGCTTAGAGCTGGCCCCAGGTGCCAGGCAGCAGGCACATTT
CCTTCTGCCCAAAAAACAAAACACACATGAATCTGAGGTTGGGCGTGGTAAGGGCAGGCCAAGGCTGACC
GTCCTATGTGGATATCTGTGAGGTAGTGTGCCTACATGTAAGGGTCTGTTGTGGGTCTACTCCCACGAAA
GCCTTCATCTTACGATGAACCAGAGAGGACTGCAGACTTGCCAAGGCCTAGCTATATGCTTGGAGCCAGG
ATTTGAAACTTGATCTTTGGGGATGCACGTGCCTCAGACTATTGGTGAGTGTGCTGGTGGGGCACTGCAG
GCTCAGGAAGCAGCGTGTCTGCATATGCTTATCTGTACACAAGTCTGTAAGAGTCCCCCTTCTCCCCATA
CAATGCCCCCATCCCTGCCAGGCTTCTTTTTGAGCTGGCGAAATAGCTGCTTGTATTCTTCTCTTCATGG
ATCATCTTTATTTCACCCAAGTTTGGGTTTGCACCTAGTGGAGCCTTGGCAAGTGGCCTTATTTGTCTCC
ACTACTGCCAGCTTTTGTAGGCTCCATGTCAATGGCACTAGGCACACAGGTAGACAGGTGGGCTGTCTCC
AGACTTCTCTATTACCAGCACTTCCCAGCATGGCCCTCACAGCAACCATGTGAGGTAAGAGGAATTTCCA
GTTTCCTGATGGGGAAACTGAGACCAAAAGAGTGAGGGACTGCCAAGGCCTCATAGCTAGAATTTAAGAG
CTGTGTGGTTCTCCTCACTAAGCTGGGAAGGGGATGGTCAGGGAAAGCTTCTTGAAAGAGCAGGAGAAGG
CAGATCTCCATCAGGGCAGGGAGCAGAGCAAGGCCCCAGGATTCTGCCTGGGGCACCAGGAAGCCTGGCT
TATGAGAAGGTTCTCAGTCCTCAGAGCTGACATGTGATATACAGTCCAGGCACAGGTGTGTGTGGTCCCT
CATTACTTCAGAGCCCCTTAAGAAAGACTGAATCTATTTCTTCATCAGAGTTTGTGAGCGATTCAATATA
AGGGACTAAATCCCCCTCACTGCCCCAAGCAGCTTATCTTGTCACTGTCTACCATAGCCACATTTGGAAT
GGTAATGCCCAGGCCATTCCTGAAGCCCAGGCAGCATTCACTGTGGGCTTGGGGACATGGTGCCATTCCT
GAAGCCTGGGCAGCCATCACCATGGGCCTGGGGACGTGGTGCTGGGCAGAATGAATATGCTGCAGCCCTG
ATGGGCTGTGCTGGCTGGGCTTTGCCTTCTTGGGTCAAGGCGAGCCTGGGCATTAGGCCTTTGTCATTAT
GCTATACATCAGGCTTCTGGGCTGCTACTTGTGGGATCCTGCCCTTGTTCTCAAAGAGTTCCTCCTTCTC
ACTGCCCCATCTTCTTCATAGTGACGGCCTCTTCGTACCCCTGGCTTTTCTTTTCCCCAGAGTTCCCCTG
AATGTTGTCCTCTCATGGTTCTGAGTTGGGGAGGAGTGCTAGGTCATGGATTTTTGGGTATAACGTGTGA
CTTTCCTACTCCCCTAAGTAGTTCTCCCCTTCTCAAGCTCCTAAGTTCTGGGAAGGTCTCTTTTCCTGCC
CTCCTGACTAATGGCAGAGAGGTCTGACCCAGACTGTGCCAGACTGGATCATTCGCTCTGTCACCTGCCA
CCAGGGCAGAGGCCATTCCTCTCTGGGGAGTCTCCTTGTGAATTTCTGGGGACCAGCTCTGGCTCTCTCA
AGAAAGAGGATGCTGCCATATTTGTTCTGGGAGGCAGGAAGATGAAGGGTGAGGTTGGGAGGTAGCACAG
GATGTGGCTTTCAAGAACCTAGTAGAGCATCTCACTGTGCTGCCAGGGCCAGGCTGGTGCCTTCTTACGG
AAGACAGTACAAGGGATCAGGTGTGGCCAACAGGAACTTGGGAGCATTGGATGCCTGGCGTGGAGCTGCG
CTATGCTTACCTGGTTCCTATCTCAGGCACCTGTTCTGCCTTCAACTGATCTCAATGGAAATATGTGCAG
GAGTGCAGGCCTGTTGACTCTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTACAGTCACACTCA
CCTTTGCAAGAAGGTGTGGGAGGGGGATGACAGCAGCTCCACACCGGAAGAGCAGACTGGTTTCTGTTTC
AAAAGGCAGAGTTTGTGGTTGTTCTGCAGTTTCTGATCTAGCCATTTCCCCTGATGGAAGCTCCTCCTTC
TGTCATTGGAAGCCCTGTGTTCTCGGTTAGGTCTTTTATGGCCCAGTTCTCCCTGCCCCTGTTTCTACCC
GAGTATAACTGTTCATTTTTGTTCCCCATCCCTATTTGGTTTTCCCTCCTTCTGCCTGTGTACCTGCCTT
TTTCATTTCTTCAGTCATTAAGCAAGCCCTGGAGGGGCCCTGCCTGGCCTTAGGTATGTGAGCATGTATG
TACGTGTTTGTATGCACGAGGCATCAAGTGTATTAGTACCACAGGAAGGAGCTTCTCAGTTGGGCCCTTG
GTGGAAGAGAAGGGAGCCGGGGAGGTGGACATTTCCAGACTAGGAATCAAGATGAAATAGGGATGGGAAG
CAACAGCTATTCTTGCCCTAGGTGTGGCTTAGTGTGGATGGAGCAGAGAGGGTGAGAGGGCAAAAGCTGG
GGAGGTAAATTCCTGAGCCCTGTCACAAAGAGCCTTCAAGGCCATAGAAGGTGTTTGTTGTTTGTTCTCC
TTAGACTGGCAGTGGGCAGCCTCGGGAGGGGCTTGAATGAGGTCTAGGGGGGTCAGAATAATGTTTTATG
AAGAGCCAGAAGACTGGGGAAGGATGGCTGATGGGTGAGAACCAGGGGTCAGGGAAAACAGCAGAAAAGG
CAGGACTCTCAGCTGGAGGACAGGCTGGAGGGGTTTGCTGAGGGGACAGGTGGTTCCAGGTAGAACCAGA
AATGTGTCGGGGAGCTAGGGTTAGGGCCAGAAGCAATGCCCACTGTTCCAGGTGGGATAGATGTGGAGTT
TTGTGACAGTTGCTAGAGGGACAGGACAGGAAGAGAGCATCTGGGGGAGTTGGGCCGTTAGGACATTCCA
GGCAGGTTGGTGTGCAGTTCGGGCTGGAAGGGCTCCTGGGGTGGGGGCTGGCCAGGCAAATGCTGGCACT
GCATCTGGCTCCGAAGTTACCAGGCCAGTCTGGGTTTAGAGGATTTTAAGAGGCTTCAGAGCTTGGGGAG

FIGURE 1 (continued)

TACTCAAAGAAAGTCATAGCTGTTGGCTAAGCCAAGCTTTTTTCCTTTGACCTAATCTACCTTAAATCGG
TGATTTCTGGGCTGGAATGTCTGCCCTCCAGCCAGCAGGCAGCCCCTCCCTGTGCTGGAGAGTGTGTCAG
AGCCTGTGCACCTTTGCTGAGGGAGCAGAGGAGTCCATTGGATGGGCCCCCTCCATGTCCCACATATAGT
GCTGGGTGTTTCTAGCTGTTACGACTTTTGATCTTACCAACATCTTTCTGATGCTATTGTGTTACTCTTA
TGTTACTCTCTTCACAGGTGTAGCAGTGAGGTCAGAGTGGCTGTCACTTTATTGAGATCACATAGCTAAT
GTGAGGTAGAGCTAGGATTTTAGTTCAGCCAGTCTCACCCAGAGCTCGTGCATGTTTTTTCTACCACCCT
GCCTTCTAGAGAAACTCAGTCAAGCCCTTTGCTTTACACATGGTAAAACTGAGACTCTGAGAAGTTAAAT
AAATTATTCATCATTGCCTCAAGTTTTAGTGGCTGAGGGCAGGTCATCTGCTATTCAAGCCCGTGTACCT
CTCTGACTATGCCTTGTGAAGGCCACGGGAGCATGCAAGGGCCTTGGATAGCTAAGATAAGGAAATGGTC
CCAGGCAAAATGGTGGTCTGGGTCCAGGATGGTTGCTGCTCTTGGACAGCCAGTGCCTTGGTCAGGGGAT
GGGGTGGGGATTAGGCCCCTTGCTGAGACTTGTGTGGGGATGGCTTTAGCAGTTAGGCATTTCAGGGATG
CACCAGTCCTCTGGGCCAGAGCCTACTTTCTCCCAGGGATCCTGAGGCCCATCTTGACCTACCCAGCCCT
GCCTCTGGGACTTTATGATTTGATTTGTGTGTACCTTGTGTCAGGAAGTGGTCCTCATGAACAGCCTTGG
GTCCCTATTTCTTCTTCTGGAGTCTAGCTCTTTTGCAGGTCAAAATGTCTCAGTGAGGGAACAAAGATAG
GGAAGGGACACCCCACAGAACCACCTTTCCCCCATATAGCCCTCTCTGACATCTCAGCCCTTACTTAGCA
AAGGCCTATCCCTAGACTCAACCCAGCCCTCTTATTACCAGAGTGACTGAGTGGTCTTGGCTCTGCCTCT
GGGGTTCCTCCCTGAGAGAGAGTGTAAGAATGAGGAAACCAGGCTGCCCTCCTTTCGGTGTTGACTCTGG
GAGACCCCAGCTTGATCTTGGCCTCTTTGCTACCTTCCTAGTTGACATTCGTGAAATTAAGGAGATCCGC
CCAGGGAAGACCTCACGGGACTTTGATCGCTATCAAGAGGACCCAGCTTTCCGGCCGGACCAGTCACATT
GCTTTGTCATTCTCTATGGAATGGAATTTCGCCTGAAAACGCTGAGCCTGCAAGGTGGGAGTTAAGGGGG
TAGAGGAGGTAGAGGATAGTTAGGGGAATGCCTGCTGGCTCCTGCCCAGTGGGAGGTATGTGCCCTCGGG
GCAGCTATTGATACCTTGCTCACAGCCACATCTGAGGATGAAGTGAACATGTGGATCAAGGGCTTAACTT
GGCTGATGGAGGATACATTGCAGGCACCCACACCCCTGCAGATTGAGAGGTAAGAACCACTCCTGAAGGG
GTTAGGGCTGGGAGCATTAGGGACCAGGGGGACAGGGACAGCAGACCTTTGTGTGCCCAGACATCTCCCA
GGCCTGACTGTAGATGGAGAAGTGGCCCTCACCTCAGGCTTCTCTCTCCAGGTGGCTCCGGAAGCAGTTT
TACTCAGTGGATCGGAATCGTGAGGATCGGTAAGTACTGAGCTGTGGCTGTAGCCCAGCAGGGTGGGGAT
GGGCATCCAGAACCTTAGCCAGGCCTCTAAGTAGCTGCCCGGAGAGCCAGAGGACCCAGGGGACCTTAAG
TGGGGCCAGGAGGGTGGGCAGAAGGTTCTGCCACGTGTAGCTTTCTGCACAAAGTCCTCTGGTGGCCTTG
GTGTGAGCTGGTGAGAGGAGCCAGCCACATGCTGTGTGCCCTGCCACTATGGGCAGAGACTGGATGTGTA
GAACTGGCTTTGGGTGTCCTGGAGGTGAGGGTGGCCAGTAGCGTGTGAAGGGTGCCCTGAAACTCTGGCT
CTGAGACCTGGTATGGCAGCCAGAGGGGCCAAGGAGAGAAGGGGGAGCAAAGACCAGATAGTGTGGGTGC
TGCACCATGGTGAGGTCCTTTGACCTGAAAGAAATGGGAAGCCATGGAAGGGTTCTGAGGAGAGGAGTGA
TGTGACCTGACTTGGGTTACTCAAGATCACTCTGCCTGCTGTGTGGAGAGCTCAGTTAGGAGCTGTTTCC
ACACTCCAGGTGAAAAATGAGAGGGCTTGGATCATGATGGTAATGGTAGGAAGTGGCTGGATTTTGGCCA
TGTTGTATTTTGAAGATAGCGCCAGAAAGAATGTCCTTAACAGATTGATTTTGGGGTGTGAGAGGCATTG
AGGATAATAGTATGCTGTTTGGCTTGAGCAACTGGAAAACAGAGTCACCATTGACTGAGATGAGAAGATC
ATGGGACTAGCCCATTTGGAGGGAAGCTTGGGTTCAGTTCGAGGCATGTTAAGTTTTCTGATGCCTATTA
GCTGTCCAGGGAGAGATGTTGAGTAGGCAGGTGGTTAGAGTGAGTTTAGGTACATACACAGTAGGGGCTA
CAGATTTTAACTTGGGAGTATGTAGATAACACTGAAAGCCACAGGGCTGGGTGAGATCACCTAGGGGGCA
AGCAGACCAAGAAAAGGGCAGGGTCCAGTGGCTGATCCCAGACCACCCCCATATTAGAGATTGGAGGGGT
CAGGGACAACTAGTGCGGTAAGAGGAGAACCCCCAGAGTGTTGAGTTCTGGCAGCCCAAGGAAGAAGACA
GTGGTGAAATCTGACCGTTGACCCTTGGATTTAACATGGTGAGAAGAGCGGTGTCACCCTAGCGGTGAGG
GGCTCAAGGGAATGAGAGGGAGCAAGATGACTCTTGCAAGGAGTTTTGCTATGGAGGGGAGCAAAGAAGA
GGGCAGTAGCTGGAGAGCTAAGCAGGGGCAAGACAGGTGTTTTTGGTGGAAGAAGTAACAAGCTGTTCGT
ATGCTGATGGGAAAGAGACCACAGAGGGCAAGATCGGTGATGCAGGCAGTTGCAACCAGAAGGCCTCTGT
TTCCTCACTGGAAAACAAGGACCCTGATAGCACCTACCTCCTGGGTGACTGAGGATCAGAGGAGGGGGCG
CCTATATAGAGCCAGCCCTCCCTCCGCAGTGCTTGATCCACTCAGTGTGGCGCTCAGCCCCCTCGGGGAA
TTTTGGTGCCTCCTCCCAGGCTCTTGGGGCCCAGAGGAGGTGGTCCCACCCTCCCCTCCCCTCCTTGACA
CCACCTTCCAGGAGAGAAAGCCCCCCCCTTCCCCCTTCTTGTCCATCCTGTTGCCAGGTCCAGCAGTGTC
CCCAGCCTCACATCCTGGGCAGGACACCCCTGGAGAGCAGGGGCGCTTGTTCTCTCAGTTTCTTTCCTGG
AGCCAGGCCCTGTCTAGCCCCAGGAGGTGCCCAGTTGCCAGTCATTGTATTTGGTGGAGCATGCACCTCC

FIGURE 1 (continued)

TCCTTCCTCCCTCTCATGGGTTAGTGGGTTCTGAGGACCAAACTCCCAGCATCCCAGTGGGCAGCAGGTA
GGGACCTGCTGCCATGCTGCCCCCAACAGGGAAGTTGTGAGTGAGCCCTGCCTTCTGTCTTGGATAGGCT
GACTGCCACCTTGGCACAGGCCTCAGCAGTGCCGGTAGGAGGGGAGGCCTGGAGTGTGGTTTTTCTTCCT
CCCATGCCTGACCCACTTTACTGAATCTGTTCACATCTTCCTTGCCAGAATTACAGGTTTTTTTTGTTTG
TTTTGTTTTTGTTTTTTTTTTTTTTTTTTTGCTCAGATGAGGAACTGAGGTCCAAAGAAAGGAAGGGAC
TAACCTCACCCCATGGGTTCTGATCCAGTCTTGCCCTCAGGCCTCCAGGTTCCCAGAATAGTGTTGTTTA
CCTGTCCAGCCCCAGGTGGGCTCGACCCACAGGTCAGAGGTCATGAGAAGCTGGATGAGACCACTGGGGA
TGTCCCTGTTTTCTCAGTATATCAGCCAAGGACCTGAAGAACATGCTGTCCCAGGTCAACTACCGGGTCC
CCAACATGCGCTTCCTCCGAGAGCGGCTGACGGTAAGTGCCACCCAGGGCTGTCTGTAGATGGGGGCAGG
GGAAGCCAAGAGCCCTTCAGCTGGGGGCCTGACTGCCTGACTGGCACTCCTGCTCTATACCATGCAGGAC
CTGGAGCAGCGCAGCGGGGACATCACCTACGGGCAGTTTGCTCAGCTGTACCGCAGCCTCATGTACAGCG
CCCAGAAGACGGTGCATGAGCCACCTGCCCTCCCTCAACCCCTGCCCCTGCTCTTCCACCCCACACCCCA
GCTCTGCCTGCCTCAGCCCTGCTGCCCTGCTTAGGGGCTTTTGGGTGCCATTTCTCCAGTTCTTCTCCTC
TTGAGGCCTGCCCCCATCTGCTGCTCTAGCCTGCCTTCTTACTAGCCCATTTCCCACATGGCCTCCCAGG
GGTCTTGCCCTGACCAGGTTCTGTTTCCTGCAGATGGACCTCCCCTTCTTGGAAGCCAGTACTCTGAGGT
TTGGTTTGGAGTGGGGAGGTGGGGTTTTCCCTGGGCCCCCTTCATCTCTCCACTGGGCGATTCTTGATCC
AGGTGGGAGGCAGTGGGAGTAGGGAACCATGCTGGACCATTCTGGGAAGCTGTGCTGGCTGGGAGTTGGG
TTCTGCCTTCCGTGGGGCACCTTGTTGTCTGTTGACCATACTAGCTAGCTTACCTTCTCTCCCTGCAGGG
CTGGGGAGCGGCCGGAGCTTTGCCGAGTGTCCCTTCCTGAGTTCCAGCAGTTCCTTCTTGACTACCAGGG
GGTATGGCTGGGCTGACATTGGCCCAGGCTGGTAGGTTGTGGGGGGCTGGGCTCATCCCTGACTGGAGGC
TTCTCTCATCCCCTGCCCTCCCTACCCCATCAGGAGCTGTGGGCTGTTGATCGCCTCCAGGTGCAGGAGT
TCATGCTCAGCTTCCTCCGAGACCCCTTACGAGAGATCGAGGAGCCATACTTCTTCCTGGATGAGGTGAG
CCCGATGTTTCACCCATTTTTTGTCAAGAGAATGAGTAGGGGTGACCAGGACCCCACCCGGGCTCCAGGA
GCTAGACGCTCCTTAGGGATGCCACCTTGTTTCTACCTACTGTGCACCTTGCCCACCCCCAGTTGGGACA
GAGCACTCTCTCTCCTACCCCCAACCTACCATCTTGGGTTGGACAGGGCAGGGACTCACTGTCTCTTCCC
TTCCACATGTTTCTGGACAGTTTGTCACCTTCCTGTTCTCCAAAGAGAACAGTGTGTGGAACTCGCAGCT
GGATGCAGTATGCCCGGACACCATGAACAACCCTCTTTCCCACTACTGGATCTCCTCCTCGCACAACACG
TGAGTGTGGCTCCTTCAGGCCCACCCAGCTTCTTCCCCAGGAGGGCCCATCTGACCATACCTACCTGCCT
CTCCTTGCCTATCCAGGTACCTGACCGGGGACCAGTTCTCCAGTGAGTCCTCCTTGGAAGCCTATGCTCG
CTGCCTGCGGATGGGCTGTCGCTGCATTGAGTGTGCGTGGGGTCCAGGGCTGGGGGAGGGAAGATGGGAG
GCCTGCCCGCTTGACCATGGTGATGTTGCTCCCCAGTGGACTGCTGGGACGGCCCGGATGGGATGCCAGT
TATTTACCATGGGCACACCCTTACCACCAAGATCAAGTTCTCAGATGTCCTGCACACCATCAAGGAGCAT
GCCTTTGTGGCCTCAGAGTGAGTCGGAGGCTGGATGACCCAGGGGTTAACTTGGCTCCAGGTCTCTCGTT
CTAGAGGGACAGAGGGCAGAAAGACTCCTCAAATGCCCTGTCCCCTCTCCCTCAGCCTTTCATCTTTGTC
CTTCCTCTTGGCCTCTCCTCGTCACCTGCTCCCTGCTTGAGCTGTTGCTTCCCAAGTTACACTTTCTGTT
TCCTACGTGTTGGGCCCACTCTCTTCTTCATGGGTCCTTTAGACTGTAGAACACATGCTCTTCTCATCTT
CAGAAAACATGCCCTGGTTTCTTTAGGCCAGTGTCCTGCCAACTCCTTTGCCCTCACAGCCCAGAAGATT
GTCTCTGTTCCCTGTGTCCCATTCCTTCAATTCTGTTTACTGCTTAAACTGTGGTCACTGGTCTCCCTTA
GCTCACCAGGGCTCTAACAGCTAACTTTGGAGGCTTCTCCTCTCTCCTGGCCTCTTTGGTGTGAAACATT
TTTCTTGCACTGCTGAGCAGCCTCCATAATTGGGCCAGCTCGGGACTGCATCAGTTGCCACCCTTTGGTT
TCCACTGCTGCCACAGCTGTAGAACCCCTCTCTGCCCCACCAGTGGCTATGGCCTGCCTCTTTTCTGGGA
TAGTTTTTACAGACAAGAAGCCCCCAGGCCCTTGGCTTCCAACAGCTCACTGTGAGGGGCTACTTAGACC
CAGAGAATTGCAGAATCTGTTTCACTGTGCTTGTCCCCCATCCCGCAGGTACCCAGTCATCCTGTCCATT
GAGGACCACTGCAGCATTGCCCAGCAGAGAAACATGGCCCAATACTTCAAGAAGGTGCTGGGGGGACACAC
TCCTCACCAAGCCCGTGGAGATCTCTGCCGACGGGCTCCCCTCACCCAACCAGCTTAAGAGGAAGATCCT
CATCAAGGTGGGGTGGCGGGCTTATTGCGGAAGCCCCACACTTCTCAGTGCCTTGCCCAGGCCATGGCTT
CAGCTGTTGGGCCTAAACCTGGGTGAGGAGGTGGGGTGAGGACTGGGGTCTGCATTGCCCTGTTCTGGTT
GCCCCTACAGCACAAGAAGCTGGCTGAGGGCAGTGCCTACGAGGAGGTGCCTACATCCATGATGTACTCT
GAGAACGACATCAGCAACTCTATCAAGAATGGCATCCTCTACCTGGAGGACCCTGTGAACCACGTGAGGA
CTGGGCCAGGCTGGGGGTGGTAGGCCAGTGGGTGTGAGGACCCTGGCTCACAAGTCCCTCTTTGGTCTGT
TCCAGGAATGGTATCCCCACTACTTTGTTCTGACCAGCAGCAAGATCTACTACTCTGAGGAGACCAGCAG

FIGURE 1 (continued)

TGACCAGGGCAACGAGGATGAGGAGGAGCCCAAGGAGGTGAGGAACCAGCTCAGGTCTGGGGGCTGGGCC
AGGTCAGGCCTGGGCCAGGGTCACAGTATCTTTGCTGTTGCCTTCCCCTGACAGGTCAGCAGCAGCACAG
AGCTGCACTCCAATGAGAAGTGGTTCCATGGGAAGCTAGGGGCAGGGCGTGACGGGCGTCACATCGCTGA
GCGCCTGCTTACTGAGTACTGCATCGAGACCGGAGCCCCTGACGGCTCCTTCCTCGTGCGAGAGAGTGAG
ACCTTCGTGGGCGACTACACGCTCTCTTTCTGGTAACACTTCCCATGCAGATGCGTATGTTCAGTCAGCG
TGTGTACACAGACATCACATCACCCAGAGATAATCAGTTAACATTTGAGCCTTTGATCCAGGACAATAAT
TAGGCTTTACATGGAACATAATTTCACCTACATACACACACACACTCTCTGTCTCACCCCCCCCCCATAC
CCCTCCCTTTTCGGTTCATTTGAAGCCCACACCTTTGGTTCATGTGACTGCCCACACCTGAGCTCCTCAG
GAGATTGGCCTCCCTCCTTGAGGCTCCCTCCTTGAGTTCCACCCTCATTTGGGGTGGAACTTGGTCTTTG
GGGCCCTGGCCTGTTTTCCCCAGCCTCCCTCACTCTGTGTCTTCCACAGGCGGAACGGGAAAGTCCAGCA
CTGCCGTATCCACTCCCGGCAAGATGCTGGGACCCCCAAGTTCTTCTTGACAGACAACCTCGTCTTTGAC
TCCCTCTATGACCTCATCACGCACTACCAGCAGGTGCCCCTGCGCTGTAATGAGTTTGAGATGCGACTTT
CAGAGCCTGTCCCACAGACCAACGCCCACGAGAGCAAAGAGTGAGGGAAGGGCCTGGGGGCGGACAAGGC
AGGGCAGGGCCATGGGTGGTGCTGGCCGGGCCTGACTCTGCCTGTTCTCAGGTGGTACCACGCGAGCCTG
ACCAGAGCACAGGCTGAGCACATGCTAATGCGCGTCCCTCGTGATGGGGCCTTCCTGGTGCGGAAGCGGA
ATGAACCCAACTCATATGCCATCTCTTTCCGGTGAGGGGTGTGGCACTGGGTTGTGGGGCCTTGCTTGGG
TCTGAGCTGCCCTGACCCTGTGTGACTGTTTTGTCCTTGTGAAGGGCTGAGGGCAAGATCAAGCATTGCC
GTGTCCAGCAAGAGGGCCAGACAGTGATGCTAGGGAACTCGGAGTTCGACAGCCTTGTTGACCTCATCAG
CTACTATGAGAAACACCCGCTATACCGCAAGATGAAGCTGCGCTATCCCATCAACGAGGAGGCACTGGAG
AAGATTGGCACAGCTGTGAGGGGGCTGTGGTAGACGGGGCATGGCAGGGGAGGCAGGAGAGACCCAGAAT
CTTACCAGTCTCTGGATGTGTGTAACAGCAAGACCTGGTGTGTTGTAGAAGTTCGTGGGAGGGCCCCTGA
CTCCAGCTGGGAGCCACAGTGTGGGTACCAGGAGGGTGTCTGCAGGAGGGGACATCTGAGCAGCATCTTT
AAGGATGGGGACAGGCACATAAGCAGAGGGTTCCTCATGAGTCAAGATGTGGAGTGAGGAGGTTCTGGGG
CTCACACTGGGAGAGGTGCACACAGTGGAAACTCATCCACCTGGGCTTGGCCTGGACTCTGTCCTAGGGC
AGATGAGATGAGGCTACCCAAGAGTGGTTGTGGAGCCTCCGCCTGGTGGATGGTATGGAGGGCAGAGCCA
CAGGAGGTGAGACCAGTGAGGGAAAAAGTCAGGACCCATGGCAGCACAGCTGGTGATAAGGGCCCTGGAC
AGAAGGAAGGGGTCTAGGACCAGAAGATCAGTTGAGAGACTGCTGTCGTCAGTAGACAGGGCTGGCTGGG
GAGAGAGAGGCCTGTTGTCCACTGGCACCTGGGACTCAAGTGATGGAGAGGAGCGGCAGGAGGAATGTGG
GGAGTGGGAAGGCTTTTCCTGACTTTGGGCTCAGCAGTGAACCAACAAGCCACTGAACTAAAGCACTGAA
TATGGGTAGTCTGTGAAGGGCCCACCTGCACATAGCTCAGAAATACTTGGGAGTTTGGGCATTTAGGACC
TGAGAGATTTTAGAATCCTGGGCTGGGCCTTACATGTAAGAATGTGAAGAAAGGAAAGGGAACAGTGAGG
CCGGGCCTGAGGCCTCTGAAGCCGTCTCTACTGAGGTCGAAGGATCCCTGTGGATCAGGTGCAAGTTTGC
TGCACTGGGGGAAAGGGAAGCTGCTCCAGAAACCAGTAGCTGCTTTCTACCTCTGGGCTCTGGGGCATTA
ACATATCCCATTGTGTCCTGTTTCCAGGAGCCTGACTACGGGGCCCTGTATGAGGGACGCAACCCTGGCT
TCTATGTAGAGGCAAACCCTATGCCAACTTTCAAGGTACAGCTCAGGCCTCTGGGCATAGGAAGCTGGGG
AGGGTCCCCAGCTGCTTGGGGCTTCATTTCTGTGTTCTGGGCCATCTGTGGTCTTTGTGGAGAAGTGGTG
GTTGTGGTTTTCCGAGGCCCAAGAGGTTGTGAGAGATGTGTGGTTGGTGAGCGACCGCAGGTCTCCCAGG
GCCGACCCACTCCCTAGCCCCTACCCCTTAAGTCAGCAGTGACCCTTTAAACTGCTCCTGTGGGTGACCC
CTGTTTCCTTCCTGGGCAGCAGCGGGGTAGGAGCTGGGAGGCACACTGGCCACTCATTCCCCGGCCTCAT
GGAGCCCTGTTACACAGGTTCTTTTTTGTTTTGCCTTTTTCTCTAAAAAGGCCTGGGCCCTATTTCTCAC
CCCCTCCCCTCCACAGCCAGGGGACCTGGAAGGAAGTTTTTCTTTCCACTTCACAGATGAGTGGTAGGGT
CCCATCCAGGCCCCATATGCTTCCAGGTCCCGGGGAGGCACTCAGGGCCACTGCAGACCCTGCCTTCTTG
GCCTGCCAGCCCTGACTCCTGGGAGCGGATTCAAGGTTCTCCCTGTGGCCCAGGGTGGGGCTTAAGGTTC
CACCTGGGTCCCGAGGTATTTCACTGGCAGAGGCCCTGCCTCTCTGATCATATCTGTCCTGGAGCTTCCC
TGCAGGGCAGTAACAAGAACTATAACTAGGGCCTGTTGATGGCAGTGTCATCTCCCACTGGCCTGACCCC
AGGCAGGGAAGCCCAAGCACATGTGTGTGTGCACATGAAGCCCCAGGTTGGCAGTGGCAGGGAGAGCCTT
TCTGCTCTGACTGGTGCTTCTCACCTCTGCAGTGTGCAGTCAAAGCCCTCTTTGACTACAAGGCCCAGAG
GGAGGACGAGCTGACCTTCATCAAGAGCGCCATCATCCAGAATGTGGAGAAGCAAGAGGGAGGCTGGTAA
GCCAGTGGTGTGGTAGGCCCAGAGTCCAAGGGCCCCAGTGGAGCTGGGGCCCCAAAGACATGCATTTGTG
ATGTGCTTGTCTCCTGTGTGCACCAGCAGTGCCTGCCTCACCCTGGCTTAGGCATGGGAACCCCTACCAA
AGGATACCCTCCTCATGGGAGTTCGGGGTGGTTGCTGGAGGTCAGCACCCTGTGGCTCCCACAGGTGGCG

FIGURE 1 (continued)

AGGGGACTACGGAGGGAAGAAGCAGCTGTGGTTCCCATCAAACTACGTGGAAGAGATGGTCAACCCCGTG
GCCCTGGAGCCGGAGAGGGAGGTAAGACCAGAACCACCTGAGTAACAGCATTCCCTATTCCCAGATTCTC
CTTGGCATGCCCCCATCACACAGTCCCAAGCACGCACGTGCATGCACAGACACCTGTCACATGGGCTGGT
CGCACAGCCCATGTGGCCATGCACGTAGTCTCCCATATACCTGTGCTACATTTGGCAGTCACAGGTACAC
CCACAAGATGTATTTGTCCCATGCACACGGATATCCCCTCACACACATATGCAGTAGCCATGCTGACCAT
TGGTGGGCTTTGCTTCCCACAGCACTTGGACGAGAACAGCCCCCTAGGGGACTTGCTGCGGGGGGTCTTG
GATGTGCCGGCTTGTCAGATTGGTGAGCTCCCATCTGTTTCTCTTGCCCACTGTTCCCTAGGGTGAGATT
CTTCTTTGTATCTCTTTCCTGCTCCTAGGGAGGAAGCTGATGGCTGAACCCCAAAGTCTGCCCTCACTCC
AAGCTCTCCCCATGCTCTGGACATCCCCTTGACACCCTGGGCTCCCTTTGTCACTGTCAGCTTTGACCCC
TGCATGTTTACCTATGCCAGGCACTGGGGAACCCGTCAGAATCAGCAGAACAAAGTTGATGCTGCTGGTT
GGCTGACATCCCCAGGCCTAATGGGTTGTACCACAGGGATGTGACAGAGGCTTGGAGATGGGGTGGAGAG
GGAGACACGGCCTGAGGAAGAAGCATGAGTCAGAGCTGAGTTGGAACACTGGCTCCACCACAACCAGCAG
TGACTTGTTTGAGTTGTAGCGTCGTCATCTGTCAAATGGGCCAGCAGAGTAGTCCTTCCCCTCATGGGGT
GTGGGAAGGAGGAAATGGGATGAGATAGAACTCATTTGAGCCAGTGCCTGCGGTGTGGAGTGGGGTGGAG
GGGGTGAGATGTCTATTCCCAGCTGTTATCTGCTCTCGCCCTCCCAGCCATCCGTCCTGAGGGCAAGAAC
AACCGGCTCTTCGTCTTCTCCATCAGCATGGCGTCGGTGGCCCACTGGTCCCTGGATGTTGCTGCCGACT
CACAGGAGGAGCTGCAGGACTGGGTGAAAAAGATCCGTGAAGTGGCCCAGACAGCAGACGCCAGGGTGAG
ATTCTGCTGGAACCTTCTGGGGGGCAGTGTGTGGGCCCGTCAGGCAGCTGAGGCCTCCAGCTCCCAGCAC
AGGCCCCCTCAGAGCAGTGGGGCAGCCGATGGCCTATGCTAGATAGGCCACAGCCCCTGCCTTAGCTAGG
GATTGAGAAGAAACAGACACATAAGATGCAATGTGGTGTGTTTAGGTTGTGTTGAGTTTGAGATACTGAT
GGGTCGTTGAAGTGGGTCTGCTTAGTGGGCAATTGGATACACAAGACCAGAGGTAAGAGGAGAAGTCCTG
GGCTGGAAGCAGGAGTGGAGTGGGGGCTGAGGCATAGAAGGGATGAGGTGGTGTCGCATAGGAAGAGAAC
TTGGGATGGATTGAGAAGCTCCATATGAGAAGGCATGGGCGAGGAAAGGAGCCCAGGAAAGGCAGGTCAG
ACAGACTGCAGGCCACTGGTGAGGGAGAGGGTCTGCTGTGTTGAGAGCTACAGAGGTAAAGACAGGAACG
ATAAGAACTTGCAAGTGCCCTTTGGATTCAGCAGCAGCTAATAGCCCTTGTGAGACTTTTGAGCTGCATC
AGCAGCATGGCTGGCATTAGATGGCAGTGGGCAGCAGGGAGTCTGGAATGGCAAAAGCAGAGCCTTTGTA
GGGCCTGTCCTTGAGGGAGAGAACAGGTGACTGGGGTTTGAGCAGGCTCTCATGCAGATGGCTGAAAGGA
GCGAGCAGCGTGTGGGAGGAGATGGAGCCCAAGCTTAGCTGGTAGGACCAGCCTTCTGGAGAAGGTGGCC
TCTTCCCCTGAGCCTGGGGGAACAGAGAAGTATTCTCAAGGGTTAGGGAATTCCTACTTGGTGGCCCTTT
CACCAAGTGCATTTGGTAGATGGGTCTGTAGCTGCTTTGGAGAGGGCACCCGCAAGCCAAATAGAGAAGG
GATAGGGTGCTTGCCAGGCTGTCCCCTAGAAGGAAAAGGTGCTGGCATACCAGGTGGTTGAAGGACTGGA
TCTGGGGGTCTAGGCTGAAAAGGGAAGAGTCTGAATGTAAGAGCCACTGAGGCCGGGCGTGGTGGCTCAC
GCCTGTAATCCCAGCACTTTGGGAGGCCGAGATGGGCAGATCACTTGAGGTCAGGACTTCGAGACCAGCC
TGGCCAATATGGTGAAACCCTGTCTCTACTGAAAATACAAAAATTAGCCGGGCATGTTGGCCGGCACCTG
TAATCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATCGCTTGAACCCGTGAGGTGGAGATTGCAGTGAGC
CGAGATCACGCCACTGAACTCCAGCCTGGGCGACAGAGCAAGACTCTGTCTCAAAAAAAAAAAAAAAAAA
AAAAAGCCACTGAAAGAAAGTCCTCCAGGAGAGGATGGGTTGGGGTGCTTGTAAGTGGGCTTCTGTAGAG
ATTTGGCATGGAGATTTGCCATGAAGAGTGGGTGGTTATATTTGAGTTGGGGGCGCTGAGGCAGTGAGGA
TCATCCTTAGGACACAGATGGAAACCAAGCCAGGGGCCTGTATCCCCAGTGCAGTCACAGGTAACACAGA
AGAATCATTTTTACCCCAGCATGAGGCTGGGTAATAAATGGTCAGAAAGTGTCATTTGGGAGTGTGGCCA
ATTCCAGGATCCCTGGAAGGTCACTGGGAACATGGGTGGTGATGAGGAGTCTGTATCCCCCACCCCCCCT
AAGAGGGTTGGAGGGCAAATGTGTCCTCTGGGACAGAAAAGAGGAAAGATGATTTCAGGATGAGGCTGAG
GACAGAGCTCCCTCATTTACTGTTGGGTGTGGTGTCTGGAAGGTACAGGGGAAGGTGGGAGAGGGGCCCA
GAGCACCTGCAGTGTGGGCATGCCCAAGGTTGGCAGGGGCTTCCTTCTCCTGGGCAGGGCTGTAGCCTGG
GGCTACAGGGCCTTGTGTGTGTCACCAGCTCACTGAAGGGAAGATAATGGAACGGAGGAAGAAGATTGCC
CTGGAGCTCTCTGAACTTGTCGTCTACTGCCGGCCTGTTCCCTTTGATGAAGAGAGTAAGGGCCAGGGCC
CAGGCGGGGTGTGCATGTGCCTGGAGGGCCTGGTGGGTGCAAAAAGAGTATTTAGGTATCCCCCCAACAC
TTCCTGGGTGGGCGGGCTCTGTAAGTGTTTTCCCTGTTTGGCCCAGAGATTGGCACAGAACGTGCTTGCT
ACCGGGACATGTCATCCTTCCCGGAAACCAAGGCTGAGAAATACGTGAACAAGGCCAAAGGCAAGAAGTT
CCTTCAGTACAATCGACTGCAGCTCTCCCGCATCTACCCCAAGGGCCAGCGACTGGATTCCTCCAACTAC
GATCCTTTGCCCATGTGGATCTGTGGCAGTCAGCTTGTGGCCCTCAACTTCCAGACCCCTGGTGAGGAAG

FIGURE 1 (continued)

TCCCCTGTGAGGAGGGTGAGGAGGGGCACTGTGGGGCAGCTGGACTGGAATACACCATAATCTGCCTCTT
CCAGACAAGCCTATGCAGATGAACCAGGCCCTCTTCATGACGGGCAGGCACTGTGGCTACGTGCTGCAGC
CAAGCACCATGCGGGATGAGGCCTTCGACCCCTTTGACAAGAGCAGCCTCCGCGGGCTGGAGCCATGTGC
CATCTCTATTGAGGTGGGTGCTGCTCATCTGGGCTTCAGGGTAGGAAAGGGGCTGCTTGCCGTTGGAGTC
TGTTTATGTTGAGTTCTCCAAAAGTAGGTATTTTCAGGCATCAAGGTGGTCAGGGTGGGTGGGGCCTGAG
CTGAGTCTTTGAAGGGGTGAAGATAGCATGCAGTCACTGTATGCATCTAGGACGTGCAGAGCCATGGTGT
GACTTGTTCTGATGACTTGTTTTGTTCTGATGAGATCTTTTTTTTCCCTAAGGGGAGGTCATTTAAAAGA
TTTCTGTGTTAAAATAGTAATGGATTTAACATGAAGTAGATTGCAAAACTCACATGGAAATTTTGGCTAA
AGCTCAGACTTCAGATAAACTACAGGCAGCAGCTGCTCTGGACAGCTTAGGGTCCCTGATGTCGTGAGGG
ACTCCATGGGCAGTGTCCCGGGGGCCCAGCAGAGGGCGCGCTGCCTCCACTCCACAGATGCTGACTGAGC
CTCCGCAGTGGGGAATTGGAGGGAGCAGGAAGGACAATCCCAGGCCCTTCTTTGTCTGCCTACAGGTGCT
GGGGGCCCGACATCTGCCAAAGAATGGCCGAGGCATTGTGTGTCCTTTTGTGGAGATTGAGGTGGCTGGA
GCTGAGTATGACAGCACCAAGCAGAAGACAGAGTTTGTGGGTCAGTCTGTCTTCCCAGTCATCCTCCTCA
TCCTGCTGGGGCACTGCAAGCCTCTCCCCACCAGTCATCCCATCCTCTCCCACGGTGACCTGAAGCCTTT
TGTCGTTGCCTTCACAGTGGACAATGGACTCAACCCTGTATGGCCAGCCAAGCCCTTCCACTTCCAGATC
AGTAACCCTGAATTTGCCTTTCTGCGCTTCGTGGTGTATGAGGAAGACATGTTTAGTGACCAGAATTTCC
TGGCTCAGGCTACTTTCCCAGTAAAAGGCCTGAAGACAGGTGAGGACCATTCCTGGAGGCAGTGCCCCTG
CAATCTTGCTGGCAGGGTGGGGCTGGGCCCCTTGCTCTGTCCCTCGTGGGCTGAGGGCCAGGCTTTTCCT
CCTCCTAGGATACAGAGCAGTGCCTTTGAAGAACAACTACAGTGAGGACCTGGAGTTGGCCTCCCTGCTG
ATCAAGATTGACATTTTCCCTGCCAAGGTATCTGCAGCAGGGGTGGGCTGGCCTGGGGTAGGTGGGAGGA
GAGCCAGGCAGCAGCCTCTAGAAGTGCAGAGGAGTCATTGACCCTCTTGTGCACCTGGCTTCGTTGAAGC
AGGAGAATGGTGACCTCAGTCCCTTCAGTGGTACGTCCCTGCGGGAGCGGGGCTCAGATGCCTCAGGCCA
GCTGTTTCATGGCCGAGCCCGGGAAGGCTCCTTTGAATCCCGCTACCAGCAGCCGTTTGAGGACTTCCGC
ATCTCCCAGGAGCATCTCGCAGACCATTTTGACAGTCGAGAACGAAGGTGAGGAAGATGGAGGGGTGCTA
GAGCCAGGAAGGCAGTGGCTAGGTCCTCCTTCTTCAGTGTTTCTTTCTCCTGGGTAGAAAAGTTGTAATA
TTGTCTGGCATTGGGCTGCAAGGCCCTGCCTGCCAGTAAGGACACTCTTCCCTTCTGTCCAGGGCCCCAA
GAAGGACTCGGGTCAATGGAGACAACCGCCTCTAGTTGTACCCCAGCCTCGTTGGAGAGCAGCAGGTGCT
GTGCGCCTTGTAGAATGCCGCGAACTGGGTTCTTTGGAAGCAGCCCCCTGTGGCGGCCTTCCGGGTCTCG
CAGCCTGAAGCCTGGATTCCAGCAGTGAATGCTAGACAGAAACCAAGCCATTAATGAGATGTTATTACTG
TTTTGGGCCTCCATGCCCCAGCTCTGGATGAAGGCAAAAACTGTACTGTGTTTCGCATTAAGCACACACA
TCTGGCCCTGACTTCTGGAGATGGATCCTTCCATCTTGTGGGGCCAGGACCATGGCCGAAGCCCCTTGGA
GAGAGAGGCTGCCTCAGCCAGTGGCACAGGAGACTCCAAGGAGCTACTGACATTCCTAAGAGTGGAGGAG
GAGGAGGAGCCTTGCTGGGCCAGGGAAACAAAGTTTACATTGTCCTGTAGCTTTAAAACCACAGCTGGGC
AGGGTGAGAAGCTAGATGCCCCTGCAGTTTGGCCCTGGAGCCAGGGCAGAGGAATGTAGGGCCTGCATGG
AGAAGGGTTCTGCCCTGCCTGAGGAGGAGGACACAGCACAAGGGCACATTGCCCATGGCTGGGAACATGA
CCCAGCCTGAAAGATACAGGGGATCATGTTAAAAATAGCAGTATTATTTTTCGTCTCAATGGTATTGTAA
CTAAGTTATTTACTCCTCCTGCTCCTCACCCCTGTAGGGAAACCTTGGAGAGGAGAGTGGCAGGTGGGCT
GCCTGCTGTGTTAAGAGGACTTAGTTTGTGATGTAAGGCACTGTCAGGAATGGGGGGCGGGCCAGGGTGG
GAAGAGAAGAAATAGCAGAGCCTATTTTGGTGAGGTTTTTTGTTTTTAAGTCAAAGAAGACTCAGTATGC
TTTCCCTGAGGAATGAAAAAGGGATTGAGGAGTTGCCTGACTCCTGGGTGGGTGGGGTACAGGCAGTTAG
GTGCTGAATGAAGCTGCCATCCTTGCTGCAGCTTCTAACTGGTAAAAAGATCCAGGGATGGAGATGGGAA
GGTTAGAAAGGCAGCCCTCACCTCTGAGGACAGAGGCCGGGGTCCAGGCCCGTGGGCGCAAAGGTGCCTC
ATAGCATAGCCAGCATTCAGCACACACAAACCTACTGCCCACATTTGGGCTCAGGGTTGGCCATTTGCTA
GTTCTGCTGCCCTCTTAAGATCTGACTGCCAAATAAATCATCCTCATGTCCTTTTTCCTTTGACTTGTAT
GCTCTTTCGGGGGCTCAGGAAAGCCTGTTGCATGGGACATGCTCACTAGAAACAGTCGCCAGATGATTAT
TCTGCAGTAGAAGCAGGTAGGAAATTTCTGGAAATTTCTCAGGTTAAGCAGCAAGAGCTGTAACCCCTCC
TCTGGGCTAACAGGAGTTGTGGGTCCACTCTCTCCTGCCCACCCTCTGAGGGTGTGTCTGAGCAGAGTAC
ATCCTGCCTGGGTTCTTTGTGGCCAGCCAGTTTTGGTGGTGAGCTGGAAACAACCAGAGCCCCTTTCCAG
TTCCACAGAAACCTCTCCTTTCAAAAATGTTGCATTCAGTTCGTTAACACTGCCAGGTGCCATTCTGATT
GCCTCTAGGACTTGGCAGCTGAAATCTCTGGGCCCTTTCAACACAGTTGAAAGGCCCTTCTCTTCCTGAA
GCTCTGTTTCCATAGTTGGCTGTGCTGGGATGGAACAAAAATGACGCCACACAAAAAATTTAAGATAGAT

FIGURE 1 (continued)

CCGGTTCCGTGGATGACATGAACTGATGATAGCCAGTATCAAACAGCGATAGTGCTCAGGTTCTTGTGTG
ACTTTCTTTTACAGCTTCACAGTCCCAGTTCATAGAGAGGAGGGTGGCTTTTTCCCATACACAAGAAGGT
GGTGGGTGGGAATTCACCTGGGCCCTCATGATCCATGTTTCCTCTCTAGGTTTTTATGGCCTGGAGAGAA
AGGTTTCCTATCAGAGAAGGAAGAGGACTGTGTAGGCCCTTCTGTTAGGGCCCATCCACGTTGGTTAGGA
CGTCCTTGGCGTGTTTGTTAGTGTTGACCCTTTTAGTTTTCATCAATACGTATCTCTATTTGCTGAACAA
GTGTCTTTCTGGAACACAACCTGGGGAACAGACAGCTCTGCCTTTCTTAAGGCAGCTTTGTAGACCTGAG
GCTCACCTCTCTTGGGCTCTGTAAGACATTGCCTTTGCCTCACTGCAAATGTTTTGATTGTTCTTCCTAG
TGGAAAACGTGCCAACTCTCAAGCAAATTTAAAGATCATTTTCACTTCAAGATTCCTCCAGACCTGACAA
ATGTTGATTGACCCAGAAGGCAGAGTGTTTGTTGGTGGGGAAGACCCTTACTTGGGGCCGAATGCTTTGG
CATCAGGAGTTGTTTGCCCCATCCCATGCATGCAGGCCGTGTCCCTACAGTGCGACAGCTCAGGGTTATG
ACCTGTGGAGTCTCAACCCTAACAGCACATTAGCACCACTTGGGGAGCTTCTGAAAAATACTGGTACCCG
GGGCCTTAGCATAGGTATTGTTCAAAACCTCTCAAGGTGATTTAAATGAGTAACAAGGGTTGAAAAACCC
TGATTTTGGCAGCACAAACCAAAAGAGCAGGCAGGGCCGGGAGAGGGAAGTCAGTGGTACCAGAAGGTAG
ATGGGCTCCCTTGCAGGCTCCTTGTTCTCCTGCCATCACCAGTAGAACCTTCTGGCTGACAGACCAGGGA
CAAGTAGACTGGGTTCAAAGTGACAGACCTTTCACTTTCAACAGCTTTGGCTCAGCAGACATGTACACAT
ACAAAGTAGAGCCTACAAGGTCAGGGGCATTCTGCCCCCGCCACAGGACTAAAGACTGCCCTGCGGGAAG
ATGGCAGGAGCAGTTTCTGACCTCAGTTGAGTATCTGTGGCCATGAGCAGAAAAGGCAGGGGTCTGCCTC
CTGACCAAGCACATCTTGAACATCACCTGAGAGCTTGAACATCACTAAGGACCTAGACACTCACTTGTCT
TTCAACTTGAGCCCATCACTCACCATGTGAGTTCTGTTGAGGGTGGGTAGAAAGCAAATAGGTTCAGGTT
ATCCCACCAGACTAACTCGGTGAATGAAAGGATCATGCCTTCTTCACATTTTAATTAAATGGATCAAGCA
CAGTCTCAGACTGCAACTCCTGTCTTCTCTGGGTACTTTAGTAATTCCCAGGGGACTTGTGCTTAGGGGT
TAATCTAGGCATTCTGTTCCCTGCCTGGAGGAACCCCACAGCAACCCCCCTGGCTGGCCGCTCCTGCGAA
TTCCACCCATAGTATCCCAAGTGAGTCACTGCCTGAGTCTACCCACTACAGCATTCAGCTGATTGGCTTT
GCCAGTTGCATGCCAGTTTGGTCTAGTTTCCAAGGACCTGGTTTTTGGGATTCAACACACACAGCTGCTT
CCCCATGACATAAGCTGGACTCCTATTCTGGTGTCCAGAATCACTGCCTGGCTCCACTGTAGGTGATTTC
ATTTCAAAGGACCCTTTTTCCTTCTGTCCCAGGCCTTCAGGGCCACCCCAACAAAATTCAAATGCTTTGG
GTCTTAGAAGCTGGGGCTTTAGTCTTTTTCCTCCAGAAAGCCCCTGGGTCCTTATGCATATTCCCTAACC
CCCGACACCGCCCCAGCAAATGACAGGCTATGCTTTTCAGCACTCTCACAGGAAACAGAAAAGAACTTGC
CAGTGTCCTCTCACCAGATGATACCAGGTTTGACTGTTTGCCTTTGTCTATTTAGCATAATTTCTAAAAT
ATCATAGTTTTCTCATGTAGAAGCCAGTGTGGTGATCTCAGCAATGCAGAAGACAGTGAGTTGGAACTTC
TCTGGTGAGCTGAGGGAAACTGCCCCACTCATCCACTGGAGTTTAAGATCCACAGAAGTGGGCAAGAACA
AGTGAAATGTTTTTGGCTTTTTTCCTGACTCCCCCACAAAATAAGTCAGCAGATGTGAAATATATTTATG
TTTTTATTTAGGAATAATCAAAAGGTTTGAAGTACCATTGAGGCCCATTTCAAATTGTACAAGCAATTTG
TCCGTGTTCCCCTCCCTTATCCAAATCCACAGATACAAAATCTAGGAAATGTGCAATTTGCATCTTAGAA
ATAGCAGCATCCCCACAGGGGACCTCGTGAGGCCTGGAGATTCAGCCCCAAGAGGGCAACCCCACTCCTG
CCTCAGCACGACCACAGTCCAAACCGAAGTTAAGTTCCATTTTTTTGTTAAAACGTTTACCCAGGGTAAA
GAATTCCCATTCTACCCAAGGCTTAAGTGATAGAGTATGCTGTTTTCTCGGTTTGGTCTCTCACACCTGG
CCATGGCAGGAGATGGGACCCTCTTGCAGAGTTTGGCTAAAGTTTCATTGTGCCTCAAAACAAACAAAAA
CAGGGCAGTTGCCTCTTACTTGTTTAGCACCAAGATGATCACCTTTTCAGCCATCTCTCCTGACAGCAGA
CTGCTCAACAGTCACTCCCCAGTCTTATTGCCCAGAAGTCCGGCCACAGGGAACAAGGCTTTGTGCTGAA
GACCAAAATGCAAATGGGTGCTAGAAAACCAGGAATCAAGACCTTGTCAGGAGGCATCTACAGGCCTTTG
GCAACCTCCCTGACTTCCACAAAGGCTGCCCTCAGTAAAACTCAATGAACAATGGCCAGCAGGGGAGAAA
GGAAGGTGGGCGTGTTTTCTCTTTAATAACAATTATGGCACAATCTGACCCTCCTAACACTTCTGAACAA
AGCAACTGCTCAGAAGCACAGCGGGAACCCTCTACACAGGGGTGACTGCTTCTCCCCTGGCCCCGACCCA
GTCTAACCGAGAACAACCGGATTGCTGTGCTGGGTCCCTGCTGAGGAGTAGGGACTGGCGCTCCTCACTC
CTGCTGACAATCTCATGTGGGGCTCTGGCCCTGTTCCAAGCAAACTGCAAGAACGAGACCAAACAGTATG
GGCAGGAACCAGGGATGAGTGACAAGATCTCCCTAAACAAATTACAGGATTCATAGGTACCATGTAGATT
TTTCTTTTAAATGTATTTCTACTCAGGTTTGATTCTTGGGAAAGACCAAGCACTTGTAGCTCTCTATTCA
GTGACTAAACAACCTGACATTTCACTTTTAACTCCAGTCACATTAAGTTTTTTTTTTTTTTTTGAGACGG
AGTTTCGCTCTGTCGCCCAGGCTGGAGTGCAGTGGCACGATCTCAGCTCACTGCAACCTCCACCTCCCGG
GTTCAAGTGATTCTCCTTCCTCAGCCTCCTGAGTAGCTGGGATTACAGGCGCGCACCACCACGCCCGGCT

FIGURE 1 (continued)

AATTTTTGTATTTTTAGTAGAAACGGGGTTTCACCATGCCGATCAGGCTGGTCTCGAACTCCTGACCTCA
GGTGATCCGCCTCCCTTGGCCTCCCAAAGTGCTGGGATTACAGGTGTGAGCCACTGCGCCCAGCCAAGTC
ACGTTAATTTTGAATCATCCACTTACGGAAAGGAACAGAAGTTAAAAAGCATTAACCAAGAAAAACTATT
CATTAACACATACAGGTGCTCATGTGTGTGTGTGCACGCGCACATGAACACACGTTTCAAGCCAGTCTCC
TGAAGGAAGAGGCACTAATGGCAGGTAAATGCTCAGGCTCCTCTCAGTACCCTGGGGCTCACCGCCTATC
CAAGTGGACAGCAGGGAAGGTGCCTAGAGTCCCCACCAGAGCGGCTGCCTTCCTCCCTTCGCTCAGCTGC
CAGAGCAGCCACGAAAGCCAAATTCTCAGGGCTGTGGAAGCTTTGGACCAGCAACAACAAGCTAGTACCT
ATATGTTCTTTATCATCCTCAAAGTCCTGCGAACCCAAAGATAGAACTTTCAGAAATTGAGGAAGGGGGT
GCTTTCCCCTGTCCTTGTCCATATGGTAACCAGGGTCTGCCTAGTCTCATCCCCAGCCTCTGGGTTCCCT
CCCCTGCTCTAGACTTCAGGGCAGTTAGAATGGATGACTCTGCTGGATCTAGAGCTAAATAGAAACTTCT
TTGCCATAGAAACTTCTCTGTTGAAGGACTGCGTCCCCATTCAAAGAGGTCAGATTTGTGGGCAGGCAAG
AGCTCAGGAATGAAGAACCAAAAAGGAGGCTCTCAACCCCTCTCCAAGGCCAGACGCTCTCTGTACTCCC
ATTAACTTCACAACCAAGTGCAGACGCTCGGTGAGTTCAGAGACCACTTGGTTAGCCCTGCCCCACCCCT
CCTGGTGTGACCTGGCACTGGGAACACACAGATTGCAGCAGAAACCTGTTGGTTCCATTTGCACTCAGAG
CAAACCAAGCAGCACCTTGATTGCCACTTTTCCTCCAGCCACTCTGTCAAAATCAAAACTGGTTGCCTCA
CCAGCCCTGGTGTGGCATGGCCCAACCATGTCCCTGCCGCCCCACTTAAATGGCCAGAGAAAACTACATG
GTGGGTAGATGAGGTTGAAGCCTTGCTTGGGGAAGGGACTTGAGCACAGGAGAAAGGCTTGAGCTCCACA
ACTGCCCATTTGCTCAGACAATGGAGCTTTTCTGAGATCAAGTGCTCCCCAAACTACATGGGAGTAGCCC
CCCGTGGTCTGGGCAGGCTGGCTGAGAGAGGTCTGTGCTCTCAGGTAAAAGGAGAGAAGGAAGCTGGGTC
AAGAGACCCTGAAGAGGAGGGTCCGTGTCTGGAGTGAGGGGAACTGAGCCCTGCTGGCTACCTGACCTGG
GTGGGCTGCTGGCTTTGCCCTGGAAGACTTGACTATGTGGGCCTTCATGTGTCTAGAGGATTTTTCTTCT
CCAGCATATAACTACCTTGAGAATGGATGTGATATGTGAAAATTTAAATTTAATACAAAAGCACATCTGC
AAATGGTGAGTCAAACTGGTGAAATCTCCCAGGTAAACTCTGAGCAAGAAAAAAGAGAAGATGACTTTAG
GAAAATCCTAAACGAGGTTTGGTTTTAAAATTTTCTTCTTGGCTGGCTCTCCTCTCCTGCAAGTTGCCTT
TATCCACTTGGGGTGTGATATCTGAACTGAAAAAGCTGCACCAATCTGAGGATATTGGTCCAAAAAGAGA
CAAGAGACCACGAGGCTCAAGCAGAGAGCATCCACACAGCATCCAACCAGAAAGGCCAGTGTCCTTCCTC
CATGAAAGGCAGCCAGGGACAGATGTCCCAGAGCCAGGAGAGAGAGGGAGAGAACACAGGACCTGCCCCT
AGGCCACTGACTGAGCAGGATAAAACCCACAAGGGCACATCTCAGGCTACGGAATAGAGAGATTTCCTGG
TGGGACGGCCTCCCAAGGCTAGCTGGAGATGAGACCACTAGTACATGTGTGAGCCCGCAAGGCACTACCC
AATGTTCTGTCCAACTTCCTCCTTGTGCTACTAGAGAGCACAGTGTGGAGTCCTTGTGTCAAGGTGCTTT
GGTCCACCTGAACAGCCACCTGTCACTCAGCCAAGAGAAAGGAGCTTTAAGTTGTACAATCACTACCAAA
CCCCAAGGCCCTGGCAAGCCATCCAACTAGGGCGTTCTTTTTCAGGAACCCAAGATTCTCAAAAATGACA
CTCCTCCCCTCCCAAAATAAAAAAGCTCCTTTATAGTCAAAAACGAAAACAAGTAATCAAAATATACAAA
GCATATGTATCAAATTTAAATTTCCTTTATCAGAATGATCATCTGGTTTCACCTTTGAGAACTCGATCTA
CAACCCCATGTAAAAAACAAATGGGTACAAGACATCAGCAACAAAAAAACACTAAAAGATGATTTTACTA
TCTCTGACGAGTCCAACTGCATACAGAGAAAAGGGATAAGATTAGCCACTTTTTATAGGCTTTTTCTTCA
GGAGAGACTAACCTCACCCAACTCTCAACTCTGCAGCCCACAAATGCCTTCTACTGAAGGCAACAACACA
ATTTAACCCTTAGGCAGTGTGCAAAACCACAGTGAGCTGTCCTGTGACAGGGCTACATACCTGGCTGCTG
CCATCCCACATCCCCCACTGCCACTGGGCTAGTGTGGGTGTGTCTCTGTGCACGACTGGCTGGATTCAGG
GTTTTGCCCCCAAACCCTTGAGTACCTCCTACAATGTCCCTTTAAGCACCTGCGTGATGACTGCCTCCCT
CATCATCGCTTTTGATCATCTTTCAAGGATAAGGTCCAGAGCATACTCACTCACTCTCATCCAACAGCAG
AGGAAGAAGGATCTGTCCAGACTGCTGGGCTCCTTACATGGGCATTCTTGCCTTTTGTAGTGTAGCCCTG
GCTGTTGGGCAGGGCTAACATCTATAAGAAAAACATACCAGGGCAGGCAGCACTGTACTTTTCCACCTGA
AAGATGAGCTAGTGCCCATGGCTGGGTCACTGTAGGTCCTGCATGAACTTGTCCACCAACTGTGTTTTGC
TGTTTGGGTTGTAAATTAACCGTGAATACAAGTAACCAAGAAAATCCTCTCCACAGACCAACTCTTCAGC
CAGTGCATGCAGGGCTCTGGAGGTGATGCCAGCAGGATCTGGAGGTGAGGCACTGGGTGGTTTCTCAGAC
ACCCGGAGATGGCTTCAGCCTGGGCCGCCCCAGCTGCCTAGTGCACTGGTGTCCCTCCAACACAGGCTAC
TCCCCCAACACCCATGTGCCACCAAGTTTCTCAACTGCACACGCCAGATGCGCGTTTTACGAGAATCAAA
TGAGTATTTATACTGTATATGTGTGTGTGTATATATATATATATATAAATTAATCTGCACGTATATAAACAC
TAAAAGGAGAAATTCCAAGTGTCTGTTCTCTGAAGGAAAGCAATCACTCGCCATTCTTGGCAATTCCTCA
AAGGTTTTTGAGACCAAACATCTTTACTCCCCAAATTAAGAATACAAAAATAGGCTGCAAAACTTGCCAA

FIGURE 1 (continued)

GTACTCACAAGTCCCTGTTTGAGACAAATAAGATGTGGTCCCTATTGGGACAGGGAGGGCAGAAGATGAC
ACTTTAGAAGAACATGATTTTGGTTTCAAAAGCAAGACCTCTCCTGGAAGGCAGAAGGGGCCACCGCCAT
GCTTGTCCTTGGAGCCACATGAGCACGGTGCCCTGCCAGGTCCAGTTCCCTGGGTAGGGGAGAAGGACGG
TCCCTAAAACACCACCAGTGCTTCTTGCCCAAAGCCCTTGCCCTCTCTCTGGGGTCTTCTAGCACTGTCA
CTCTGCCCAGCCCAGGAGGTGTCTGTGCCCACGAAGCCTGGTACTTGTGGCTTGGCACTCTGGGAAGCAG
GTGGTTTCTAAGAAATGAGCGGAGCTACAGGTGGACAGGTCTTTAGTTCGCCCCTCTTTACCAGCTACTC
TCAGAGCAACCGGTCTTGGGGAAATTGAGGATTTACCATTTAGAACAGCTCTGTAAGCAAGTTTTCTAAT
TTTCAAAGGCACCATTTCCTGTAATTTTCTCAATTCAAAAAAGGACATGAGGGTTAGGCTAAAGTAGAGT
TCTTGTTTCCAAGTTTGGGGACATAAATATAAAACTTTAAAAGCATCCTCACAAGGACCAGTGATGCCCA
GCACCCTTGGGCATGCATCCAGCACACCGGCCAGACCCTGGGGTGGGAGCCACGGGCACTCTGGGTGTTC
TGCCAGGGATCTCTGCATGCAAGTCTTTGTGCTAAAGACCACCCTACCTCTGATAATTCCAAGAAGTCAA
CAAATCCCTCCAGCCTTCACCCTTACTAATGGGCCAGTGTGTTATTCCTTCCCAAACCATAGGAGGCTCT
GAAATGAGTGTGGAGAAAGGGCTCTGAAAACCGCAGTGGTCAAAGCTTCAGGCTGTGGCTATAGATTTCC
ACTTACGTCCCTACCCCATGTCTTTTTTCCATCTTTCTCTCACTCCAAACATGTCTAGATTAAAAAAAAA
ATGCAGGCACATAGGTCAGCACATTAGGCTTAACAACAAATGTTTCTTTAGTTGATCTGATAACTGAAAA
GTTATGGTCCATGATTCAAACTCCCATGAAAAAGCAGAATTACGGTAACAACTAAAGAGAATGGTAAAGC
ATCCAACGCTAATCACATTGCCAGTCCATTTTTTGAACTGAGGGTTACAGCAGGTTCTGCACTGAGTAGC
CCACAAGGCAAAGCAAGCCTGACATGAAACGTAGCCGGTCATCACTTAATGCAGCAGAGATCTCTTCAAA
GGTACTGCTTCCTTGAGGAACACAAAGGGGGCACAAAGGGGTTCCAGACGTAGCTTTGTGCCTATAACTT
CCCTGCCTGACTGTGGAAGGTGAGGGGCACCTGTGACCCAGCAATCCCCAGAGAACAGACACAGGTCATT
TTTAGAGATGACGTAACTGACAATGCACTGCTTGGCTAACCAAAGTTTCTACGTAATGACAGTGTTGATA
ATCTGATGTTTTATTTAACATATAGAGGTGGATGTATATGTTAAAAGCTTGATTCTGTGTCTATGAATAT
GACTATGAACTCTGAACTATTTTATCCATTGGAAGGTAAAGGAAAGGTCCTACATTGTGGGAGGAAGAAC
TGATGAGAACCCCATCTTGCTTGCTGCTTGCTTGGTGGTGGGCAGGCCGAGGGTAGCGGCAGGCTCTGGG
CTGTCTGCGAGGATTCTGGAAGCTCTCCCAGGTGCCCAGCAGCCGGGCATGGGAACGGCATGTGGCAGCA
GAGAGTCGGGTTTGGCTCTTCCACGTGGCAGGCGGTTTCCCAGACTGGCCAGTCCTTCACATTAATCAGA
TCAAATTCAGTCTGTTTCTGAGAAGAAAACACATGCCTGTCACTCTACGGCAGCTGCCACCACCTGCCCC
CCAGGCAGCCTGGTCCTTGCTATACCAGGGTGGCATCACTGGCTTTGAGGACCTCTTAATTCCATGAGCA
ATGAATGGCCTTCTGCCACCCACTCCCCCACCCTCCAGCCTGAGGGAATGTGGGTTAAGGACAGGATGCT
GGCTCAACCTTGTAAGGCCATCAGACTCTCTGAGAGACCCTGCTAAACCCTAGGCCTAGCAGCAGGAGCA
GTGGTTTGGCCTCTCCAGGCCCACTAAATCCCCCTAGCTCCCCAGGCTTCCGCCACCACCGTCTCTGGAG
TCCTGTCCTAAAATGCTTCATCCTGCCCTCTCCTTCCAGGCTCTCCAGAACATACTGTTCCAATATAATA
GCAGCTGGGTCTAGTTCTGATATGTATTCTACTGATGTCTTCACTTCATTTGTAACTTGCAACCCTAACA
TCAAAGTCAAAGTAAGGCTGATATCAGAGAGGTTCATCATCTGTGATTCATAAAGAAATGGTCCTTAATT
GCAGCTGGCTGAGAAAGCCATGAGAAACCAGGTACAGATAAACAGATTGGCCCTTCCTGTACCCACAGTT
ACCTGTCTCAGACAGAAGAGAACAATGCCAATGGCAATGGCCACCCCCTGCCATTCCTGCTCTGTCCCAC
AAAGGACAGCAACATGTCACTTTGTGTTGGATTTAGTAGCTGAGGGGAGCCAATGCTTGTCATTCAAATC
CACTCATCACATTTCCATGTTGACTTTAAGAAAAAAACCATGGTAAAATATAAATAACATAAAATTCACC
ATTACGACAATTTTAAGTGTACAATTCAGTAGCATTAAGTACATTTACAATGTTATAAAACCATCACTCT
ATTTCCAGCAATTTTTCATCATCCTAAACAGAAATTATATATCCATTAAACAACAACTCCCCATGTCCTC
CACCCCTTAGGCCCTGGTAACCTCTATTTTACCTTCTATCGCTATGCCTTTGCCTATTTTAGATACCTCA
TGTAAGTTGAATGGTACAATATTTGTCTTTTTGTGTCTTGACATCTCACTTAGCAAAAATGTTTTCAAGG
TCCATCCATGTTGTAGGATATATCAGAATTTTATTCCTTTTTTGGCTGAATAATATCTTACTGTATGTAC
ACACACATTTTCTTTATTTATCTGGTGGTAAGTACTTGTTTCCGCCTTTTGGCTACTGTGAATAATGCCA
CTAAGAACACTGATGTACATGCATATGTGAGTCCCTGTTTTCAGTCCTTGGGGCGTATACCTAGGAGTGA
AATTGCTGGATCACATGGTAATATTCTATATTCACCTTCTTGAAGAACCACAAAGTCGTTTCCCAAGGAG
CTGTACCATTTTATATTCCCACCAGCAATGCACAAGGGATCCAGTTTCTCCACATCCTCCCAACACGTTG
TTTTCTCTGGGTGTGTGTTTGTAACAGCCATCTTAAGTGTGAAGTGGTATCACGCTGTGGTTTTGATTTG
CATTTCCCTAATGCCAAAGGTTCGTCTTTTCATGTACTTATTGGCCATTTGTATATTTTCCTATGAGAAA
TGTCTAAATCATTTGCCCGTTTTTGAATTGGTTTTGTTGTTCAGTTTTAGGAGTTCTATACATATTCTGA
ATATAAATCTCTTATCAGATGTATGATTTTCAGCTCTTTTCTCCCATTCTGTGGGTTCTTTCATTCTTTT

FIGURE 1 (continued)

AACAGTGTTCTTTGAAACACAAAAGTTTTAGATTTTGACGTAATCCAAATTATTATTTTCTTTTGTTGCC
TATGCTTTGAGTGTCATACATAAGAAATCATTGCCTGGCCAGATGGGGTGGCTTGCACCTGTAATCTCAG
CACTTTGGGAGGTTGGGGAGGAATGCTTGAAGTCAGGAGTTCAAGACCAGCCTGGGCAACATAGCAAGAT
CCTGTCTACACACACACCCACACACAAAATAGTAATAATAAAATTAGCCAGGTGTGCACACTTGTAATCC
TAGCTACTCAGGAGGCTAAGGTGGGATGACTGCTTGAGCCCAGGAGTTTGAAACTGCAGTAGGTTTGATT
GTACCACTGCACTCCAGCAACAGAGCAAGAACCTGTCTCAAAAAAAAAAAAAAAAAAAAAAAAAGTAATAA
TTGCCTAATCAAAAATCTGGAAGGATTCTATTTTCTTCTAAGTATTTTATAGCTTTAGCTTTTTTTAGTT
CTTTGATCTATTTTAAGTAAATTTCTGTATATAGTACAAGGTAAGAGTATAATTTCATACTTTTGCATGT
ATATATCCAGTTTCCCAGCACCTTTTGGTGAAAAGACTGTCTTTTCCCATTGAATGGTCTTTGCACCCCT
GTCAAAAATCAATTGACCATTACGTGGGGATTTCTGGGCTTTTTATTTTATTCCATTGGTTTTGTATGTC
TCTCCTTATGCCAGTACCACACTGTTTTGATTACTGTAGCTTTGTAGTACAATTTGAAATCAAGTGAGTG
TGACTCCTTCAACTTTGTTTTTTCTCAGTTTGTCTATTTGGGGTCCCCTGAGATTCTATATAAACTTTAG
GATGGATTATTCTTTTATAATTGATAGTTTACATATTTATGGGGTACATGTGAATATTTTTTACATGCAC
AGAATGTGTAATGATCAAGTCAGCATATTTAGGGTATCCATCACCTTAGTATTTATTATTTCTGTGTGTT
GGTAATATTTCAAGTCCTCTATTCTAGCTACTTTGAAATATACAATATGTTGTTGCTAACCATAGTCACA
CTAGTCTGCTATTTAACATTAGACTTTGTTTCTTCTATCTACTATAAGTCTATACCCATTTACCAACCTC
TTTTCATTTCCCCCTTCTACTCTCACACCCTTCCCAACCTGTGCTATCTATCATTCTATTCTCTATCTCC
ATGAAATCAAGATTTTTAGCTGCCACATATGAGTAAGAACGTGTATTTGTCTTTCTGTGCCTGGGATATT
CCAATGAACATAATGACCTCCAGTTCTATTATTTTTTGTCTTTTTAATAATAGCCATTCTAACTGGGATA
AAATGACATCTCATTGTGGTTTTGATTTGTATTTCCCTTTTGATTTGTGATGTTGAGTGTTCTTTAATAT
ACCTATTGGCCATGTGTATGTCTTCTTTTGTGAATTGTCTATTCATGTCTTTTGTCCCCCCACCCACCCC
CACCTTTTTTTTTTTTTTTTGGACACAGGATCTCGCTCTGTAACCCAGGCTCTGGAATGCAGTGGCACAA
CCACGGCTCACTGCAGTCTCAACCTCCTGGGCTCAACTGATCCCCCCACTTCAGCCTCCTGAGTAGCTGG
GACTACAGGTATGTGCCACTACACCCGACTAATTTTTGTAGAGATGGGGTTTCACCATGTTGCCCAGGCT
GGTCTCAAACTCCTGGGCTCAAGTGATCCACCTACCTCGGCCTCCCAAAGTGTTGGGATTATAGGTGTTA
GCCTCTGTGCCCCACCTTTTGCCCACTTTTTAATATGATTTTTTGTTGAATTCCTTATATATTCTAGATA
TTAGTCCTTTGTTGGATGAATAGTTTTGCAAATATTTTCTCCCACTCAACATATTGTCTCTGTGCTGATT
ATTTCCTTTGCTATGCAGAAGATTTTTAATATAGTTCCCTTTGTCTATTTTTGTTTTAGTTGTGTTTTTG
AGGTCTTAGCCATAAAATCGTTGCTCAGACCAATGTCCTGAAGTGTTCTGCACTGTTTTCTTCTAGTAGT
TTCATAATTCAAGGTCTTATATTTAAATCTTTAATCTGTCTTAACTTTTGTATATGGTGAGAGATACAGG
TCCAGTTTTATTCTTTTGCTTATGGATATCTAATTTTCCCAGCATCATTTATTGAAGAGGGTGTCCTTTC
CTCATTGCATGTTCTTGGCACCTTTGTTGAAAATCAGCTGGCTGTAAATATGTGGCTTTATTTCTGGGTT
CTATTTTCTTTTCCTTTGGTCTGTGGGTCTATTTTTATACCAATACCATGTTGTTTTGGTTACTATAGCC
TTGTGATATATTTTGAAGTCAGGTAATGTGATGCCTACAGCTTTGTTCTTTTTGCTTAGGATTGCTTTGA
CTATTTTAGCTCTTTCGTGGTTCTGTACAAATTTTAGGGTTTTTTTCTACTCCTGTGAAAAAATCACATT
GGTATTTTGATAGCAATTGCATTGAATCTGTAGATTGCTTTGGACAGTGTGGCCATTTTAATATTAATTT
TTCCAATCCATAAGCTTGGGATGTCTTTCCATTTGTGTCCTCTTCAGTTTCTTTCATCAGTGTTTTACAG
TTTTCCTTGCAGAGATCTTTCACTTCCTTGATTAAATTTATTCGTAAGTATCTTTTTTTATTTTTGGTAG
CTATTGTAAATCAGATTACCTTCTTGATTTCTTTTTCAGCTATTTTATTATTGGTGTATAGAAACTCTGA
TTTTTGTACGTTAACTTTATATCCTGCCACTGTGCTGAATTTGCTTACCAGCTTTAAGAGTTTTGGTGGA
GCATTTTTGGTTTTTCTAAGTATCAGATCATGTCATCTGCAAAAAGGGACAATTTTTCTCTTTTCCAATT
TGGATGCCTTTTCTTTCTCTTGCCTGATTTCTCTGGCTAGAACTTCCAGTACTATGCTGAATAGGAGCGG
TGAAAGTGGGCATCCTTGTCATGTTCCAGTTTTCAGAAGAAGGATTTTCAGCTTTTCCCCATTCAGTATG
ATGCTAGCTGTGGGTTTATTTATGGCCTTTACTATCTTCTTTCTATGCAGTTTTCTGAGTGTTTTTTTTT
TATCATGAAGCAATGTTGAATTTTATCAAATGCTTTTTCTGTTTATTGAGATGACCACACGATTTTTGCT
CTTCATTCTGTTGATGTGATGTATTGCATTAACTGAATGGTGTATGTTAAACCATCCTTGCATTATAATT
TTTTGAGACAGAGTTTCGCTCTTGTAGCCCAGGCGGAAGCACAGGGGTGCAATCTTGTAGCCCAGGTGGA
AGCACAGGGGTGCAATCTCGGCTCACTGCAACCTCTGCTTCCTGGGTTCAAGCAATTCTCCTGCCTCAGC
CTCCTGAGTAGCTAGGATTACAGGCATGTGCCACCATGCCTGGCTAATTTTGTATTTTTAGAGATAGGGT
TTCACCATGTTGGCCAGGCTGGTCTCAAGCTCCTGACCTCAGGTGATCTGCCCACCTTGACCTCCCAAAG
TGCTGGAATTACAGGCATGAGCCACCATGCCCAGCCAAGGATTATTGATATGTGAGGTTTTGTTATTGTT

FIGURE 1 (continued)

ATACTGTTGTTTTCTAGTTGTTTTATATATTTTTTTCCTTTTTCTTTTGTTTGGCATTGTACTCTGGTAG
TTTTCTGTAGTGGTAGCATTTGAGTCTTTTCCTCATCTGTGTGTTTGCTTTGCCAGTGAGTTTTATACTT
TTGTGTGTTTTACATAGTGTTAAATGTCATGTTTTCACTTCCATGTTTAGGACTCTTGTGAGCATTTCTT
GTAGGGCCAGTCTAGTGGTGATCAATTCTCTCAGCTTTTGCCTGTCTTGGAAATACTTTATTTCTCCTTC
ATTTATGAAGGATAATTTTGCTAGACATAGTATCCTTGGCTTACTTTTTTTCCCCTTCAGCCCTGTCAAC
ATATTATCTCATTTTCTCCTGATCTGTAAGGTTTCTGCTGAAATCCACTGTTAGTCTGATGGGGCTTCCT
TTATAGTTGCTTACACACATTTCTCTTGCTGTCCTTAGAATTATCTGACTTTAGAGAGTCTGACTATAAT
GTGCCATAGAGAATACCTTTTTGCACTGTATCCATTTAGAGGCTATCAGGGCCTCCTATATCTAGATGTC
TAAATCTCTTGTGAGATTTGGGAAGTTTTCACCTATTAATATTATTTCATTAAATAGGTTTTCTCACTCT
TTCATTTTCTCTTAACCCTCTGGGATCCCAATAATTTAGATATGTAGTTGCTTTATTGTGTCCCATATGT
CACAAAGGCTTTGCTCATTTTTTATTCTTTTTTATTTCTGAGTTATGTCAAAAGACCTGTGTTCTAGCTC
TAAGACTTTTTTTTCTGCTTGATCTAATATATTGTTGAAGCTTTCAATTGTATTCTGTACTTTGTTTCAT
GAAGTCTTCTATTCCAGCATTTGCTTTTTTATGACATATATCTCTTTGATAAAATTATCATTCATTTCCC
AAATTGTTTTTCTTTTTCACATTCTCTTACATCTCATTGAGCTTCCTTACACTCAATAATTTGAATTCTT
TTTCTGGGATTTTGTGAGTTTATTTTTTATTGGAATCTATTGCAGGAAATTTATTGTGTTCCTTCTGAGG
TGTCATATTTCCTTGCTTTTTCATGTTTGTGTCCTTATGTTGATATCTGCACATCTGGTGTAACAGTTGT
TTCTTCTAATTTTTTGCATTTGCATTTGTAAGGGAGGACTTTTTCCTAGACGTATCTATGGTGTTGTTTG
GGTAGGACACTTTGGCTTTGATTCTTGGTATGTGCAGTAGTGTAGTCTCTGTATGATTTCTTTGGCTATA
AATAGCATCAGTGGTATCTGTGATTTCCTCAGTGGCTGAGTAGTTACTAGTGGAAGCTATGGTAAAATTT
TGCTAAGGACTGGAATGCCAGGTGGGCCATTCTCCAGGCACCAGTGGTAGCAGCAGTGGACAGAGCATGC
CTGTCTTTGGACCTCAGAGGAGCATACAATGGCACCAGTGTTAGTGGGTTCAAGCAGGCTGATTCTTGGG
CTTTCGGGTGGCTTACTCAGATGTCAGTAGTGGCAGCAGTTCCCAGGCATGTGATCAGGTTCTCAGGCCC
CTGGGCAGCTGGCGTGGCATGGGAGATGGCAGTGACAGTGTTGAAATGACCCTCTGGGTCCCAAGTGATA
TGTGCTTGTGTTGGCAGTGGCTGCAACAGGCTGGGCGGCCCATTCTGCAGGCCCACAAGTGGTACATACA
GGTAGTAGTGGCCAAGTGGGTAAGCCCCAACCTCAGGTACCCAAGAGGAGTATTCAAGTGCCAATGGTGG
TGGACTAGGCTGGACAATCCCCCAGCCCCTAGACTGTGTGCTCTGGCCACGGAGGTGGTGGTGTAAAGCC
AGGCTGGGCAGTCTCATCTTCAGGCTCCCTATGATGTGTGCAGGTGCCAACCAAGGTGGGCAGGTGCAGG
GCAATCCCTAGGCCACCTTCAGAATGCTTGGATAGGGAGTGGCAGTGCTGTACTACTACCTTCCATTGGA
GAGCACAGGGTTGCTGGCCAGTGGGGAATGCATGTGCCACTCACACCTCACTCAGCTCCAGTGGCACTTG
TGCCTCAGCCCCTGCTATGGTAGCTGGCACCATAGTTGTACCTCAGCCACAACAACAGGAGCACATGCCT
TGTAGTGCTTCAGCCCCAGCTGCAGTAACCCAGTCACTTATGCCTCAGCTCTGGGGAAAACAGTCTGCAG
TTCTCTTACACCTCAGCCCTGGCACTCAGGGACTCCAGGACAGTGTACAGTCTTTTGGGGGGTGGGCTTT
AAATGGCATCTTGCTGTAGCTGTTTTGTTCTCAGGAAGTGTGGGGGACCCAGTGCGAGCTCCGTTCTGGA
GCAGTTCCATTGAACAATCTCCTGGCACCTCCTATGTTAAGTTTCAGGGACTGCAAGGGCTGAGGAGCTC
TCCCGTGGCTAGAACTGCAGAATCCTTTCATGGTGGAAATGTGGACCACTGAGGGTCTCTCACTTACCTT
TTCCCCATGCTGGGGGGTCTCTCTCAGTTCCCAGCCAATCCCAGCTGAACAGGCTGCCTTGCTTCTTTTT
CCTTCCTTACTTTGTTTCCTGTCTCTTTTCCGTGAATTCCAGTGTTCTGTCTTGGATAATCTATTCAAAG
TGTGATTATCTACTCTCTATTTTTGTTCTTAATGGAAGAGGCGAGTACAAAATGCCTCTAGTCAGCCATT
TTGGTTGGGTCTTCCTGGATTTTCTTATTTCTGTAAAAATGCGACTATGCTTTTGATAGATTTTACATTG
ACTCTGTAGTTTGCTTTGGGTCACGTCTACATCTTAATATCAATCCATGAACATGGGATATCTTTCTATT
TATTTAGGTTATCTTTAATGTTTTTCAGCAACATTTTGTTGTTTTCAAGATACACTTCTTTGGCCTCCTT
GGTTAAATGTATTCCTAAGCACTTTTTCTTTTTGATGCCCTTGTAAATGATACCATTTTTAAAATTTTCT
TTTCAGATTGTTCATTGCAAGTGTATAAAAATACGACCAATTTTTTTAGACAGATAGGGTCTCACTATGT
TGCCCAGGCTGGCCTCCTTGAATTCCTGCCTCAGCCTCCCAAGTAGTGGGACTACAGTTATGTCACTGTG
CCCAGCTAAATACAAATGATTTTTTTTGTTTTTATATCCTGCAGCTTTGCCAAGTTCATTTATTAGCTCT
TAACTATTTTTGTGTGTGTGTGGATTCAAGTTTTTTTTTTGTTGTTGTTGTTGTTTTTGTTTTTTTTTTT
TGAGAAGGAGTCTCGCTCTGTCACCAGGCTGGAGTGCAGTGGCATGATCTCGGCTCACTGCAAGCTCTGC
CTGCCAGGCTCAAGTGATTCTCCTGCCTCAGCCCTAACCCTGAGACTAAAGGCACATGCCACCATGCCCA
GCTAATTTTGTATTTTTAGTAGAGACGGGGTTTCATCATGTTGGCCAGGGTGGTCTCGATCTCTTGACCT
TGTGATCCACCTGCCTTGGCCTCTCAAAGTGCTGGGATTACAGGCGTGAGCTACCACAACTGGCCTCAAG
TTTCTACATATATGATCATGTCATCTGTGAACAAAGATAATTTTACTTCTTCCTTTCGAACTTGGATCCT

FIGURE 1 (continued)

TTTATTTATTTTTTTTGCCTAACTGCTCTGGCTAGAACTTCCAATGCTGTTTTGAATAGATGTGGCAAAA
CTGGGCATCTTTATTTTATTCCTGATCTCAGGGGAAAAGTTTTCGGTCTTTCCCCATTGTTGAGTATGAT
GTTAATTGTGGGCTTTTCATATATGGTCTTCATCATATTGTCATATTCCTAGTTACTGAGTGTTTATTGT
CATGAAAGCAAGTTGACTTGTTAGATGCTCTTTCTGCTTGAATTAGGATGATGTGTTTTATTCTCTTTAT
TCTTGTAATGTGGTGAATTACATTGATATTCATGTGCCAGGCAATCCTTGCATTGCAGGGATAGATCCCT
CTTGCTCATGAGGTATAATCCTTTTAGTATGCTGCTGAATTTGGCTTGCTATTTTGTTGGGGATTTTTGT
ATCTATATTCATAAGAGATATTAGTCTGTAGATTTCTTTTCTTGTAGTGCCCTTGTCTTGCTCTGGTGTC
AGGGTAATGGTGACCTCATGAGTTAAGAAGTGTTTACTCCTCTTCAATTTTTTTGGAGGAGTTTGAGGAG
AACTGGTGTGTTAATTCTTCTTTCAATATTTGGAAGAATTCACCAGGGGTCCTAGACTTGTCACTGTTGG
AATGTTTCTGATAACAATCTTCTTACCAGTTATTGATATATTTTGGTTTTTTATTTATTTGTCAGTTGAT
TTTGGGAGAGTGCGGGTTTCTAGGAATTTCATCTAGGTTACCCAATTTATTGGCACATAACTGTTAATAG
TAGTCTCTTATAATATCATATTCATGTGAAAATATCTTATATTCATGTGAAAATGTAACATCCCCTCTTT
CCTTTCTGATGTTAGTAATTTAAGTCTTCTCTTTCATTCTTATTTAAAGGTTTGTCAATTTTGTTTTTTC
AAGAACCAACTTTTGGTTTCATTGATTCTCTATATCTGCTCTAACCTTTATTTCCTTCCTTCTGGTAACT
TTGGGTTTCATTTGCTCTTTTCTAGTTCTTTAAAGTGTACATTTAGTTTACTGATTTGAGATCTTAAAAA
AAGTTTTTTTAAGACATGGGGTCTTACGCTGTCACCCAGGCTGGAATGCAGTGGTGCAAGTATAGCTCAC
TATAACCTCAAACTCCTGGTAAACAATCCTCCCACCCCAGACACCTGAGTAGCTGGCACTACAGGAACAT
GCCACCACACCTGGCTTATTTTTTACTTTTTTGTAGAGACAGGATCCCACTTTGTTACCCAGGCAGGTCT
CAAACTCCTGGCCTCAAGTGATCCTCCTGCCTTGGCCTCCCAAAGCACTGGGATTATAGATGCAAGCCAC
CATGCTCGACTGAGATTTTTTATTTTTTGAGAAGGAGTTTCGCTCTTGTTGCCCAGGCTGGAGTGCAATG
GTGCGGTCTCAGTTCACTGCAACCTCTGCCTCCTGGGTTCAAATTATTCTCCTGCCTCAGCCTCCCAAGT
AGCTGGGATTACAGGTGCCTGCCACCATGTCCACCTAATTTTTGTATTTTTAGTAGAGACAGGGTTTCAC
TATGTTGGCCAGGCTGGTCTCGAACTCCTGACCTCAGGTGATCCACCCACCTTAGCCTCCCAAAGTGTGG
GGATTACAGGCATAAGCCACTGCGCCCAGCGTAAGTTCTCTTTTAATGTATGCATTTACAGCTACAGATT
TACCTCTTAGGATTGCTTTCACTATGTGTCATAAGTTCTGGTATGCTGTGTTTTCATTTGTCTCAAGGTA
TTTTTTACTTTCCCTTATGATTTCTTTGACCCATTAGTTTTTAAATAGTGTGTTAATTTCCACCTATTTG
TGTATTTCCACTTTTTTATTTTCAATGTCTAGTTTCATTCCACTGTAACTGGAATGTACTCTGTATAATC
TCAGTTTTTAAAAATGTATTAACACTTGTTTCATGGCTTAACATACGGTTTATCCTGGAGAGTATTCCAT
GTGAATTTGAGAAGACTGTGTATTCTGCTGTTGTTGGGTGGTATTCTGCTTATGTCTATTTGGTCTAATT
TGCTTAGAGTGTTGTTGAAATCCTCTATTTCCTGATTGATCTTCTGTCTGGTTTCTATATCCATTATCGG
ACATGGAATATTAAAGTCTCCAACTATTTTTGTCTTTCTCCCTTTAATTCTGTCATTTCTGTTTCATATG
TTTTGGAGCTCTGTTAGGGGTATATATATATATAATATATATAAATAAATATATAAAAATAAATATATAT
TTATAATAAATATATTTTTATTTCATATATAAATATATATCTTATAAATATATATATTTATATAACATAA
ATATATATTTATATATATTATATATTATATATAATATATATTTATATAAATATATATATTATATATAATA
TATTTATATATAATATATATTTATATATTATAAATATATATTATATATTATAAATATATATTATATATTA
TATATTATATAAATATTATATATAATATATATTATATATAATATATATAAAAATATATATATTTATATAT
ATAAATATTTTATCAATATAATATCCTTGTCTCTTGTAACCTTTCTTGATTTAACATTTATTTTGTGTGC
CTTTTTCAAAAGAGGACACTGGAGGTGAAGAAGGAAGCTCTTGACTCTCCTAAAGCTGATCCCAAAGTGA
AGGCTTTGAAGGCCAAGAAGGCAGTGCTGAAAGGCATCCACACAGCCACCAAGAAAAAAAAAAAAAAAGAT
TCACACATCACCCACCTTCCTGTGGCCCAAGACATTATGACTCTGAAGACAGCCTCAATATCCTCAGAAG
AGCACTACCAGGAGAAATAAGCTTGACCACTATGCCATCATCAAGTTCCCAATAACCAGTGACCACTGAG
TCTGATGTGAATTAGATAGAAGACAACAATACACCTGTGTTCACTGTGGATGTTAAAAGCCAAAAAGTAC
CAGGTCAGGCTGTGAAGCAGCTCTATGACACTGATGTGGTCAAAGTCAACACATTGATCAGGGCTGATGG
AGAGAAGAAGGCGTATGTTCAACTGGCTCCTGATTACAATGCTTCTGAGGTTGCCAACAAAACTGGGATC
ATCTTGGCTGAGTCTTGCTGGCTAATTCTAAATTATATATATATAACATGTTATACATATATTTTATATA
TAATTGTATATATTTAAAATACATATATATTTTATATATAATTGTATATATTTAAAATACATATATATTT
TATATATAATTGTATATATTTAAAATACATATATTTTATATATAATTGTATATATTTAAAATATATATT
TTTATATATAATTGTATATATTTTAAATATATTTTATATATAATTGTATATATTTAAAATATATATATTT
TTTTTCTCCAGAAAAAACAGATTATTTTGTCTGGTGATAATATAGCCACCTCAGCTGTCATATGGTTACT
ATTTTCTAGGTGTATCTTTTTCTATCCTTTTACTTTCAACCTCCTTGTGTCCTTATATCTAACATGAGTC
TCTTAAGACAGCATATAAACACTATTTGTTTAACTCCAATCTGCCAATCTTTGTTTTTAATAGAAGAGCT

FIGURE 1 (continued)

TAATCCCTTTACATTTAATGTGATTACAGATCAAGGATTTACTTCTGCCATTTGGCTATTTGTTTTTTAAT
ATGTCTTATATGTTTTTGATTCCTCAATTCCATTACTACCTCCTTTTGTATTTATTTGATTGTTCACAAT
GTACTGTTTTGATTCTGTTTTTACAATGCACTAATTTGTTAGTTTTACTATTTAGACAGATTACATCTTA
CATTCTATGCCCATTAATATAGATTTATAATTTTTTAATGAATTTGTCTTTTAAATTATAAAGCACAAAG
AGAAAAAGTTATAAACCAAAAGTACAATAGTACTGGCTCTTATATTTACCTCTAAAGTTATCTTAACTAG
TGCTCTTTTTTTTTTTTTTTTTTTTTTGTGATGGAGTCTTGCTCTGCCCCACCCAGGCTGGAGTACAGTGG
TGCGATCTCGGCTCACTGCAAGCTCTGCCTCCCAGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCAAGTA
GCTGGGATTAGCACCACCAGGCCCAGCTAAGTTTTGTATTTTTTGTAGAGATGGGTTTTCACCATGTTGG
CCAGGCTGGTCTCAAACTCCTGACCTCGTGATCCACCCGCCTCGGCCTCCCAAAGTGCTGGGATTACAGG
TGTGAGCCACGGCACCTGGCCTATTTTTTCTTATGGCTTCAAGTTTCTGTTCAGTATCCTTTCATTTCAG
CATGAAGGACTCCCTTTAGCATTTCTGGTAGGGCATGTCTACTAATAATGATCTCCTTCAATTTTATTTG
GAAATGTCTGGATTTCTCTTTCATTTTTGAAGAATAGTTTTGCCATATACAGAAATCTTGGTTTAGAGGT
TTTTTTTTTTTCTTTTTTTCACGACTTTAGATATGTCATCTCACTGCCTTTGGGCTTCCAAGATTTTTGA
TGAGGAATCGGCTGTTAATCTTGTCAAAAATTCTGTGTGACGAGTTGCTTCTCTCTTGCTGCTTTCAAAA
TCCTGTCTTCAGGTTTTGACAATCCTAATATAACATGTCTTGGTGTGGATCTGAGTTCATCCTGCTTGGA
TTTTATTGAGCTTTTTGGATGTGTAGATTCATGTCTTTCATCAGATTTGGGAAATTTTCTATCATTATTT
CTTTAAATATTCTTTCTGTCCCTTTTCTTTTTCTGCGATTCCTATATGAGTATATGAGTATGAATATACT
AATGAATATAATAACTATATGAATATATGAGTACATTAGTATGCTTGATGATGTCTCACAGCTCTCTCAG
GTTTTTTTTCCTAAATATTTTTTTTCTTTCTTCTCCTTTGGATAATTTCAATTATTTTCTCTTCAAATTC
ACTGTTCTCTTCTTTTGCATGCCCAAATCTTTGTTGAATCCCTCTAGTGGGTTTTCCATTTCAGGGATTA
TACTTTTTAGCTCTAGAATTTGTTTGGTTCCTTTTTATAATTTCTATCTCTTTATTGATATTCTCATTTT
GTTCATGCATGGTTTTCCTGATTTCCTTTAGTTCTTCGTCCATGTTTTCCTTTAGCTCGCTGAACATACT
TAAGATAGTTGATTTAATGTCTTTGGGTAATAATTCCAATGTCTGGACTTCCTCAAGGATGGTGCCTGTC
AATTTTTTTTCCTGTGAATGGACCATGGTTTTCTATTTCTTTTTATGTTTTGTAATTTTTTGTTGAGAAC
TGGACATTATGAGTATTACATTGTGGTAACTGAGAATCTAATTCTGTCATGCCTCAGAGATTGCTGATTT
TTGCTTATTGAGGGCTGGAGCCAACTATTTGTGACTTTTCCAACTATTTTTGTGAAGTGTGTATTCTTTG
CAGTATGGGGTCAGTGAAGTTTCTGTTGTGATATCTCTGTGGTTAACCAGTGACCTAAGATTTCCTTAAA
TATCTGGCTTGCCAAAAGGAGGAATAAAGAAAAAAAAAAAATAGGTACTGTCTCTTTAAATCCCCTTGTGG
CTAGAAAGCTCCCTCTGCCCAAGGGCATTGAGACAATGATCAGCCTCTGCACTGGCCCCCTCAGTGATTA
AATGCAGTAATCAGAAATCAAAAAACTCTTTTTTTTTTTTTTTTGCAATGGAGCCTCACTCTGTTGCCCA
GGCTGGAACGCAGTGGTGTCATCTTGGCTCACTGCAACTTCTGCCTCCCAGGTTCAAGTGATTCTCCTGC
CTCAGCCTCCCAAATAGCTGGGATTACAGGCACTCACCAACATGCCTGGCTAATTTTTGTATTTTTAATA
GAGACAGGGTTTTACCATGTTGGCCAGGCTGGCCTCAAACTCCTGACCTCAAGTGATCCACACCTCAGCC
TCCCAAAGTGCTGGGATTACAGGTGTGAGCCACCACACCTGGCCACAAAAACTTGACTTTTGGAGGACAA
AGTTGTTATTGCCTACCCTGGCACCAACAGTCTGCACCAGGAACATTTTCCACAGTTGCCTGCTGCAGAG
CTTGCGGATGCTGAAACAAAAAAAAAACCATCAAAATTTGTAAGCCTCTCCATCAAGCTCTTCCCTGGATG
TTGCAAGTGTTCAACTAGACTTCTGAGTCCCAAAACAGTTGCTTGAGACAATTACTGCCAGCTCAACTGC
TTTGGTGGAGGAAAAGATTCCTGGTGCTGCTACTGCCATCTTCCATAACATCATTCTCCATGTCAGCTTT
CGTAATCAACTTGTTCAAACATCCTCATCTCTCTTGAGCATGACACCCTGGCCTACTGGTATATTACAAG
AAGCACAGAGCTGGGTATAATATAAGGACCAACTTACAAACTTGGACAAAGACTTGTAGGAGAGACTACC
TGCTCTGCATTATAAAAAAGTTAAACTAGCCATAAAAACCTGTTGTTCTGACTCCAGGGTGTGCCATCAG
CTACTTTATAAAGCAGGCTGTGAGCTGTGGGCCCCAAAGGAGGGGAGTGTTTTGTTGTTGCCGTATTGAA
AACATGGCTGGAGTTGGAGGAGGCTGTAAGGGAGCCAGTGGCCCTTGTACTCCTACCCTAAGTGCTGACC
AGGGCTTTGGGCTCCACCAGGTGTTTGCTCTCACTGTGGGCTTTGTGGAACTGGATTTTGCCTTAGTATG
TTAATATGAGAAGAACAGGCTTTCTGCAAATGCTAAACAGATGGATGACATGGTACTCCCCGCCCCCAAC
CCACCAAATTATGGGCCAAAAAGGAAGTCTCTTTTTCCTTAATTCAGTAAAGAAACAATAGCATAACTAT
GTTTCAAACTGTTGTGTTCAAATGAATTTAAAATATTCAGAGAAAGAAAAAGAATTTTGTCCTTTTTAAG
ACATCCTAAGTAGAAAGCAACTGGGGTGGAGGAGCTGGGATTTGCCAGGCCAAAATAAACAAACAACAAT
GGTTGGCTATTGTATGGAAACAATGCAACACCATCCAGGAAATTCTGTGGGATTTCTGAGGGATAGGCCA
CTATGGTTGGCCCTGGGGATGAGGTACCAAACACAAGGCCCCACACTGAGGCAGCTCATGCCAAAGTCAC
CACGGAACCATCACATTGCCCAACACCACAAATAGTGTCTCCTGTACCCCCTCCCACATTGCCAACTCAG

FIGURE 1 (continued)

CTAGCAATGCTGCCATTTTGGAACCCCCAATCCCTTCAGCTTCTACAATACTCCGCCCTCCTGGCTCTCA
CCTGAGCTTCTGGCTGCCCTCTGATGGGGTCTCTAATGAGAACACAAATGTCAAAGGGTAAGGAGGGAAG
GGAGAGGCTGGGAACTCAGTGACCAGGAACCTAGAAAATCAACACGTAATAACATGACTTGTCTGTGGCT
TCAAAACTATGTCTTAAATAAAAATAATCTTCTATGATACATTTTGCTTTCGAGTACAATCCAGAGAAAC
TGAGGAACAAAATTCAAGCTTTTGATTCCATGTATGTCAAAGAAGGAAGGTGATTTTCCATTATACTAAA
CATTTCTTCTACATCAGGCATAACCAGAGAAACACAAGACTTTCATCATCAGAAAAAAGCACATTATGTA
TCTAAGGACAATTAAAGGCTCTCTTTCCTTTTCATCAATTTGAGCTGAATTTCAACTCATGTCCTGTTGC
TGTCTCCTACCCAGTGGCTGTGGATCTGCCCGACTCAGAGGATGTTTTGACCTGTTCTCCTATTGCTAAG
AAATGGCTAGAAAAGCTTGGACCCCTTTAGGGTCACCATGTTCCTTCCCCTGCGCAGGTTTTTAAAAACA
CATGAAACAAAAAACAGCTCTCAACCGTTTATCATATTATATTCCTATGGCTTCTGCTGCTAGTTGTCCT
CTGAAGCAGCCAGGCGGTTAATGCTGCTGCCAGGCAGCCTTAGAGACAGCAGATGCCCCTGTGCAGTAAA
TTCAGTGCCCAACCATAAGTGCCTCCTCCCCTTACCCACACAGGATAGCCATGGCCCCTGTGGACTCCTT
ACCGAGCTGACGTCCAGCCTGGGGACTCGATGTGTCAAAGGGCTCTGAGCTGGCCTCAGGGACACGGGGC
TCCCACGACTCACTGTTCTCAGACACCTCTGAATAGGTGTCACCCATCCCTTTGTGAACTGCTGTGAGCT
CACCAGTACCAGGGCCCTGGTCCTCACTGCCTGTGTCTGCCACGGCTCTGGTCTCCTCCCCCATTTTCTC
AGCAAACCACTGCTTGACCTGCTGGGAGCTCATCTGGGTCTTGTCACAGAGGTTCTGCAGGTCCTCTTCA
TACAGCATCTTGTGTGTCATGTAATAGTCCTGCAGGAGCTCCCGGTTGCCAGGGGCAATGACCAGTAGCC
CTGGTGGGAAGTTGCCTCGCTTATAGTCTTCGTACCATTTGAGTTGGCCGTTCTTCAGTGCGTACCTGCT
ATCTCCAAACCAGCGCACCACCTCTGGCCGTGGCAGACCCGTCTGGGCCATGATGGAGTCATAGTCCTGG
TTGCTTGGCCACTGTGTCTGGACAAAGAGCTGCCGCAGCAAGTGCCGCTGCTGGGCAGTCTTTTTGCAGC
TCACTTTGCCTGGGAGCTGCTCTGCCAGTTTGTTTGACTCATCATCCTCAGGGTCACAGGCACCCAGCCC
TGGAATCTCGTTCCTGCCATTGGCTTCAGTGACCCTCAGGTTCTTCAGGTTGATTTTAATGGGGCTGACT
TTGCGCTCTGCCAAGATATGGCTGCTGGGCATTTCCAGAGAGCCATTTTCACCAGAGACCCTTAGCTCAC
TGGCCAAATCCTCTTCTCCACCCTCATCCTCAGCAGCCTCCTCTTCCTCCTGAGAGGCATTCTCCTCAGC
CTTCTTGGTCTCCTCAGCATTCACTTTTTTCCGTCTCTCTGAAAACCAGCTATCAATTTCTCGTCGGGTC
ATTTTGGTTTCACTTCTCAGGCGGTCCAGTTCCTCATCAAGAGGAAGAGGGTTTTGTGCAAAACTGCTCT
CCAGGGCTCTGAGCTGCTCAGGGGCTCTCTCCTTGTATTTGGTTGGTGTGAAGTCAGGAGTCTGGTGCCA
AGATTGTCGTTTGGCAGAAGGGTGGGTTGCTAGTGTGGCTGTTGTCGGAATGCAGGTTACCTCAGGGACC
TTGGACGATGGGGAGAAGGACACCTCTGGCACAGAGTCAATGATGATGGAACTGTGATCTCCAGGTATCA
TCGCTCTGGAGCCCTTCAAGTTCCGGCAGTGGTATCTACGATCACTGAACCATTTCCGCACCTCTCTGGT
ACTGAGGCCCGTCACTTTTGTGAGATGTTCAACTTCGCTCTGCCCTGGGAACTGGTTCCGACAGAAGCTC
CCTTTCAGAGCTGACAGCTGTTCATGAGATTTCTTATTTTTGTAGATGCTAGCATCAAGGAAGGCTTGGG
AGGTTATGCTGGGGCAGGCCGTGAGGAGCGACTGGGCCGCATTGACCACCTTCACAGCTGACGTTGTATT
TGAACACACAGTGTTAATGGGTGCCACACCTGGCTGCTTGGGGACGGATGTCACCGTGAGGGGGAGAGGG
GAACTTGTTGCTTGCAACCCATTGGCCATCAATGGCTGAGTGACCAGAAGTCCCCCTCCTGTACCCTCTG
GCTGCCCCACAACGTGACCTGGAAGAGCGGCCTGGATGAGATGCTGGACATTGCCAGCACTGGCGACGAG
TGGGGTATTTAGAACCGTAATTGTGGGCTGAGGCACAGACTGGATGACTGTATTGAACATCTTTTTCCGG
GCATCCTCAATCTCCTCAGGGGACCAGCTGATCCCCTGCTTCAGCCTTTGGGCTGTGAACCAGATCTTGA
GCTGTTCTTCTGGATACTTGGTCACCACAGTCAAATAGCAGAGCTCGGCTTTGGTGGGGTAGGGGAACTT
GTGGAAGGAGTTCTTCAGGAAGCTGTTAGAGTCCATGGCTGCATTGTACGTTGGAATGCTGCTCAGGGGG
ATCATCACTTTGGGAAGGGCCTTGGCCGTGGGCAGTGGCTGGTGGACATGGTGTTGGGCATGCACTGGGG
GCTGCTGCTGGAGGGAGAGGAACTGTGCTATGCCAGCTGGCAAAACTGGCACTGTTCCTATCAGGGGCCC
GTTGGCGGCATGGGGGTTTTTTGCAGAGCTGGCAGATGCCTGGCTGACTGGAACTGCCCCATTGATGAAG
GAATGGTCCCCCTCTCTCACCTCCATTTCTCCAGTCGACAGCTTTGGTAAGGCCTCACCCACAGGCTGGC
TAGGGACATTCTCCTTGAGTGTATGAATTTTTTTGGCTTCAGCTTTGCCTTTCATTATCTTCATGATTGG
AGTTTTGGTAATGATGATTTCTGCCTGTCCATCAGCCCCTTCAGCACTGGGCTCACCCGCTAGGTCAGGA
GTGCTGGTGCTCTCAGGGATGCTCTGCTCCACAACCACATGATTGTCTGGCTTGGCCACGTTCCACACAA
AGCTGGCTTCCCCGGAGTGACATGTGGCATTGTGCAAGGAAAGCCCCTCAGGGGTTTTTGCCAGAAAACT
GCACCCACTGCATACAAAGGTTGGGTCTTTATTAAAGTCTGTGTGCTCTGAGTTCATATGTCCCACAAAT
TGGGTCATGTCATGGGATCTGAAATCGCAGTATTTACAGGAATATAAATAGCCATCTAAAGTGCTCCGAT
GCCCATTGGCCAGTGTAGAGCCATCAGTACTGCTGGGGTTCTGTGCTGCCTCACTGCTGGCAGCAGATGC

FIGURE 1 (continued)

TTCTGGGGGCAGATCCTGCTGGGGTCCTTCAGGCAAGGTCTCAGCGGGCTGGGCCTCCATGCTGGCATCT
TGCAACACCACAGTCTTCACTGGGATCATGCATGGTGTGGTGGATTTCCTCTTGCTGGCCATGGTGACAA
TCACTGGGTGATCAGCAGTTGAGAGCTTGTCCCATAAGGGGCCTAACAATACAAGTTCCAGCTTCTCGAT
GAGGGCCAAAGAAACAGTTTCTAAATGCAGCTTTTTCAGTTGTTTGCAGAAAGCAGGTTTTCCCTATTCA
ATCTAAGGAAAGGGAGAAAAAAATGATTAAGTTCTCTTAAGTGCTTTCTGTATATTTCTCGGATACCCAG
ACACATTCCACTGCTTGCCTTCTACCATCTAGGTCTTTTCACAGTAAGTTTAATCAGCAACTTGGATATG
AAGTCTAAGTTAGGAACCCCCTAATGACAAAAACTGGACCCTGAAGAATGACCTGGGGATGGTCCAATAC
CAACTGATAGACTTAAGCAACGTATTTTTGTTTCTTCCCCACCACCCCCTACATATCCCTGCATTAAGTA
ATTCAGATTAAAAAACAAAACGCCCTCTTTTTGGACCTCCAAATTAATTCTGACCATGTCAGAGTGAGAA
CAAAAGATCCTAGTGTAATTCTTGTTTACATTTTGGACCAACACGCGGTTTTCTTTTCATAGCCTTCCCG
CATATGAGAACAAGATGACGCCTCTGTCTGTCCCAAGCCAGGCCCAGGGACCAAGTTAGCTGCAGTGTGT
GAACGGAAGGGGTGGGGTGGGCGGGGGTGGCTAGGAAGACCGGCTGCTGTAAGAGCCAGGCCTCTGTAGC
CTTTCCTTGCCTGCCGCACTTATTCCAGGCCACAGAAAAGCGATCACCTTACAGTTACTGGCTGTTATGT
ATCCCGGACCACTGTTACTGAGATGAAACCAAAGGTCAGAGGGTCAGGGAATCCACAGAACCAGTTTGTG
GCCCAGCAAGCTATACATTTTCTGTGTACGACCACTCAAAGGGTGGTCTCACCTTGAGATCTGAGAACAG
TTGGACTGCCTCCCCAAGTGGGTCCCTGACCCCTGAGTAGCCTAACTGGGAGGCACCTCCCAGTAGGGGC
CGACTGACACCTCATACAGCTGGGTGCCCCTCTGAGATGAAGCTTCCAGAGGGAGGATCAGACAGCAACA
TCTGCCGTTCTGCAGTATTTGCTGTTCTGCAGCCTCCATTGGTGATACCCAGGCAAACAGGGTCTGGAGT
GGACCTCCAGAAAACTCCAACAGACCTGCATCTGAGGGTCCTGACTGTTAGAAGGAAAACTAACAAACAG
AAAGGACATCCACACCAAAACCCCATCTGGACGCCACCATCATCAAAGACCAAAGGTAGATAAAACCACA
AAGATGGGGAGAAACCAGAGCAGAAAAGCTGAAAATTCTAAAAATCAGAGTGCCTCTTCTCCTCCAAAGG
AACGCAGCTCCTCACCTGCAATGGAATAAAGCTGGATGGAGAATGGCTTTGATGAGTTGAGAGAAGAGGG
CTTCAGACGATCAGTAATAACAAACTTCTCTGAGCTAAAGGAGGATGCTCGAAGCCATCACAAAGAAGCT
AAAAACCTTGAAAAAAGATTAGATGAATAGCTAACTAGAATGAACAGTGTAGAGAAGACCTTAAATGACC
TGATAGAGCTGAAAACCATGGCATGAGAACTACATGACGCATGCACAAGCTTCAGTAGCCGATTTGATCA
AGTGGAAGAAAGAGTATCAGTGATTGAAGATCAAATTAATGAAATGAAGCGAGAAGTTTAGAGAGAAAAG
AGAAAAAAGAAACGAACAAAGCCTCCAAGAAATATGGGACTATGTGAAAAGAACAAATCTACGTCTGATT
GGTGTACCTGAAAATGACAGGGAGAATGGAACCAAGTTGGAAAACACTCTTCAGGATATTATCCAGGAGA
ACTTCCCCAACCTAGCAAGGCAGGCCAACATTAAAATTCAGAAATACAGAGAACAACATAAAGATACTCC
TCGAGAAGAGCAACTCCAAAACACATTAATTGTCAGATTCACCAAAGTTGAAATGAAGGAAAAAATGTTA
AGGGCAGCCAGAGAGAAAGGTCGGGTTACCCACAAAGGGAAGCCCATCAGAATAACAGCGGATCTCTCGG
CAGAAACTCTACAAGCCAGAAGAGAAGTGGGGGCCGATATTCAACATTCTTAAAGAAAAGAACTTTCAAT
CCAGAATTTCATATCCAGCCAAACTAAGCTTCATAAGTGAAGGAGAAATAAAATCCTTTACAGACAAACA
AATGCTGAGAGATTTTGTCACCACCAGGCCTGCCTTACAAGAGCTCCTGAAGGAAGCACTAAACATGGAA
AGGAACAACTGGTACCAGCCACTGCAAAAAACATGCCAAATTGTAAAGACCATCAATGCTAGAAAGAAAC
TGCATCAACTAACGAGCAAAATAACCAGCTAACATCATAATGACAGGATCAAATTCACACATAACAATAT
TAACCTTAAATGTAAATGGGCTAAATGCACCAAGCAGACCTAACTGACATCTACAGAACTCTCCACCCCA
AATGAACAGAATATACATTTGTCTCAGCACCACAGCACACTTACTCCAAAATTGACCACATAGTTGGAAG
TAAAGCACTCCTCAGCAAATGTAAAAGAACAGAAATTATAATAAACTGTCTCTCAGACCACAGTGCAATC
AAACTAGAACTCAGGATTAAGAAACTCACTCAAAACCGCTCAACTACATGGAAACTGAACATCCTGCTCC
TGAATGACTACTGGGTACATAACGAAATGAAGGCACAAAGAAAGATGTTCTTTGAAACCAATGAGAACAA
AGACACAACATACCAGAATCTCTGGGACACATTTAAAGCAGTGTGTAGAGGGAAATTTATAGCACTAAAT
GCCCACAAGAGAAAGCAGGAAATATCTAAAATTGACACCCTAACATCACAATTAAAAGAACTAGAGAAGC
AAGAACAAACACATTCAAAAGCTAGCAGAAGGCAAGAAATAACTAAGATCAGAGCAGAACTGAAGGAGAT
AGAGACACAAAAAACCCTTCAAAAAATCAATGAATCCAGGAGCTGGTTTTTTGAAAACATCAAAATTGAT
AGACAGCTAGCAAGACTAATAAAGAAGAAAAGAGAGAAGAATCAAATAGACACAATAACAAACAATAAAG
GGGATATCACCACCGATCCCATAGAAATACAAACTACCATTAGAGAATACTATAAATACCTCTACGCAAA
TAAACTAGAAAATCTAGAAGAAATGGATAAATTCCTGGACACATACACCCTCCCAAGACTAAACCAGGAA
GAAGTTGAATCCCTGAATACACCAATAACAGGTTCTGAAATTAAGGCAATAATCAATAGCCTACCAACCA
AAAGAAGTCCAGGACCAGACAGATCCACAGCTGAATCTACCACAGGTACAAAGAGGAGCTGGTACTATTC
CTTCTGAAACTATTCCAATCCACAGAAAAAGAGGGAATCCTCCCTAATTCATTTTATGAGGCCAACATCG

FIGURE 1 (continued)

TCCTGATACCAAAGCCTGGCAGAGACACAACAAAAAAAGAGAATTTTAGACCAATATCCCTGATGAACAT
CGATGCAAAAATCCTCAATAAAATACTGGCAAATCGAATCCAGCAGCACATCAAAAAGCTTATCTACCAC
GACCAAGTTGGCTTCATACCTGGGATGCAAGGCTGGTTCAACATATGCAAATCAATAAATGTAATCCATC
ATATAAACAGAACCAAAGACAAAAACCACATGATTATCTCAATAGATGCAGAAAAGGCCTTTGACAAAAT
TCAACAGCCCTTCATGCTAAAAACTCTCAATAAATTAGGTATTGATGGGACGTATCTCAAAATAATAAGA
GCTATTTATGACAAACCCACAGCCAATATCATACTGAATGGGCAAAAACTGGAAGCATTCCCTTTGAAAA
CTGGCACAAGACAGGGATGCCCTCTCTCACCACTCCTATTAACATAGTGTTGGAAGTTCTGGCCAGGGCA
ATCAGGCAGGAGAAAGAAATAAAGGTTATTCGATTAGGAAAAGAGCAAGTCAAATTGTCCCTGTTTGCAG
ATGACATGATTGTATATTTAGAAAACCCCATCGTCTCAGCCTAAAATCTCCTTAAGCTGATAAGCAACTT
CAGCAAAGTCTCAGGATACAAAATCAATGTGCAAAAATCACAAGCATTCCAATACACCAATAACAGACAA
ACAGAGAGCCAAATCATGAGTGAACTCCCATTCACGATTGCTTCAAAGAGAATAAAATACCTAGGAATCC
AACTTACAAGGGATGTGAAGGACCTCTTCAAGGAGAACTACAAACCAGTGCTCAACGAAATAAGAGGACA
CAAACAAATGGAAGAACATTCCATGCTCATGGATAGGAAGAATCAATATTGTGAAAATGGCCATACTGCC
CAAGGTAATTTATAGATTCAATGCCATCCCCATCAAGCTACCAATGACTTTCTTCACAGAATTGGAAAAA
ACTACTTTAAAGGTCATATGGAACAAAAAAAGAGCCCACATTGCCAAGACTATCCTAAGTCAAAAGAACA
AACTTGGAGGCATCATGCTACTTGACTTCAAACTATACTATACTACAAGGCTACAGTAACCAAAACAGCA
TGGTACTGGTACCAAAACAGAGATGTAGACCAATGGAACAGAACAGAGCCCTCGGAAATAATACCACACA
TCTACAACCATGTGATCTTTGACAAACTTGACAAAAACAAGAAATGGGGAAAGGATTCCCTATTTAATAA
ATGGTGCTGGGAAAACTGGCTAGCCATATGCAGAAAGCTGAAACTGGATCCCTTCCTTACACCTTATACA
AAAATTAATTCGAGATGGATTAAAGACTTAAATGTTAGACCTAAAACCATAAAAACCCTAGGAGAAAACC
TAGGCAATACCATTCAGGACATAGGCATGGGCAAGGACTTCATGTCTAAAACACCAAAAGCAATGGCAAC
AAAAGACAAAATTGACAAATGGGATCTAATTAAACTAAAGAGCTTCTGCAAAGCGAAAGAAACCACCATC
AGAGTGAACAGGCAACCTACAGAATGGGAGAAAATTTTTGCAATCTACCCATCTGACAAAGGGCTAATAT
CCAGAATCTACAAAGCACTTAAACAAATTTACAAGAAAAACATCAAAGAACCCCATCAACAAGTGCACAA
AGGATATGAACAGACACTTCTCAAAAGAAGACATTTATGCAGCCAAAAGACACATGAAAAAATGCTCATC
ATCACTGGCCATCAGAGAAATGCAAATCAAAATCACAATGAGATACCATCTCACACCAGTTAGAATGGCG
ACCATTAAAATGTCAGGAAACAACAGGTGCTGGAGAGGATGTGGAGAAATAGGAACACTTTTACACTGTT
GGTGGGACTGTAAACTAGTTCAACCATTGTGGAAGACAGTGTGGCCATTCGTCAAGGATCTAGAACTAGA
AATACCATTTGACCCAGCCATCCCATTACTGGGCATATACCCAAAGGATTATAAATCATGCTGCTATAAA
GACACATGCACACGTATGTTTATTGCGGCACTATTCACAATAGCAAAGACTTGGAACCAACCCAAATGTC
CATCAATGATAGACTGGATTAAGAAAATGTGGCACATATACACCATGGAATACTATGCAGCCATAAAAAA
TGATGAGTTCATGTCCTTTGTAGGGACATGGATGAAGCTAGAAACCATCATTCTGAGCAAACTATCACAA
GGACAGAAAACCAAACACCACATGTTCTCACTCATAGGTGGGAACTGAACAATGAGAATACTTGGACACA
GGGTGGGGAACATCACACACCACGGCCTGTCGTGGGGTGGGGAGAGGGACAGCATTAGGAGATATACCTA
ATGTAAATGACAAGTTAACGAGTGCAGCACACCAACATGGCACATGTATACCTATGTAACAAACCTGCAT
GTTGTGCACATGTACCCTAAAACTTAAAGTATAATTTAAAAAAGAATTATAAGTAATCTTCACATATGCT
TTTAAGTATTTTTTTAAAAGAAAGGAAAGAAGAAAGAAGAGGAAACCAGAAACAAATAATCATTACACTA
TCCAGACATTACATAACATCCCTTACCTGTGAATTTAGATGTATTGAACTTTTAATAAAATAGATTGACT
TCACACTTTTAAAATGCTAAGAAAGAAAACAGCTAAGGCAGAAAACTAACCTGAAAACAAAACCAATGGT
TTTATATATAAAAGACCGAAATTAAACAGTTGATAACTCAAAAAGAAATAATAATAATAATTGTTTCACA
GGATGCCATGAGAAAAGGGATTCTGTGAGCCCTATTACTAATATAGAATGATAATCATCATTATTACTTT
TCGTTTTAGCAAATCATAATGCTCTAATGACTAAAACAATAGTAATTCTAATACTAAAATCAAGTTATCA
GTATTTGGATTTGATACAAAGATGTAAAGAAAATTAAAATATCTCTATTCAAATTCTCAGTAAATAAACA
CGGCTATTTTATGATGAAAATAATTTTTAAAACTTTGAAGGTGAGGGTAAACATAAACCCACTCTAACAA
CTTCTCACCCCTTCCCCCACCAATTTGAACTGGCATGCACACTTTTTTACTTAATTTTTAATTATAAAGA
TAAAATGTAATTTAAATAAATTTAATGTCTATAATTTGGTATACCTTCTCATTTAGTCCAGATATTTTAT
TCATATTTTTATCACAATGAGCACACATTTGTGCTTTTTTCACCAAACATTACGTTATAAACCTTTTTGT
TACACAAGCTTCATAAGTTTAACATTTAATAGCTACCTAATAATGTACCACAATGAATTTGACTTATCCA
CCCCTGCTGTTGAAAAGCATGCCAATCTCATGGGTGACAGTGAAACAAACATCTCTGGGCATACAGGATG
TTTTTCTTCTATCAAATTATTTCCTGAGGTTAAGTGCACAGGAATGGGCTTACCATCTCAAAGAGCATCA
ACATTTCTAAGCTCCTTTGTATATATCATTGGCAAACATTTTAAATCAAGTGCTTTATGATCCCAAATCA

FIGURE 1 (continued)

GGGAAACTAAAAATAATACAGTTATGGACCCAGTGAGCAAATCAGATTTTCAGACAAGTTATGGAAGACA
TCAAGTAGAATATCTGAAAGCACAAACGACAAAAGAAAAAACAGATAAATTGGATGTCATCAAAATTAAA
AACTTGCATTCTTCAAAGGTCACCATCAAGAAAGTGAAAAGATAGACAATCCACAGAAAGAAAAGGTTTG
CAAATCATCTATCTGGTAAAGTATATCCAGATTATATAAATAACTTACAACTCAACCATAGAAAGATAAT
TTTTAAACGGGTAAAGGATTTGAATAGACACTTCTCCAAAGAAGATATACAAATGGCCAGTAAAGCACAT
AAAAAACTGCTCAACATCATTAGTTATTAGGAAAACACAAATCAAAACCACAATGAGATACCACTTCACA
CCCACCAAGATGGCTGTAATTACAGCGACAGATAACAAGTATAGATGAGGATGCAGAGAAACTGGAGCCC
TCACGTATTGCTGATGAAAATGTAAAATGGTATAGCCACTTTGGAAAACTGTTTGGCAAACAAAATGTTA
AATATAGAGTTGCCATAAGATCCAGCAATTTGGCCGGGCGCAGTGGCTCACACCTGTAATCCTAGCACTT
TGGGAGGCCAAGGCGGGCGGATCACCAGAGGTCAGGAGTTCAAGATCAGCCTGACCAACATGGAGAAACC
CCATCTCTACTAAAAATGCTAAATTAGCCAGGCATGTTGGTGCATGACTGTAATCCCAGCTACTCAGGAG
GCTGAGGCAGGAGAATTGCTTGAACCTGGGAGGCGGAGGTTGCAGTGAGCCAAGATCATGCCATTGTACT
CCAGCCTGGGCAACAAGAGCTAAACTGTGTCTCAAAAAAAAAAAAACCAAAAACAAAACAAAACAAAAAAA
ACAAAACACCAGCAATTTAATTCCTAAGTATATACACAGTATAAATAAAAACATGTCCACCCCAAAATAT
GTACACAAATGTTCACAGCAGCATTATTCAAATAATGGCCAAAAGGTGGAAACAACCCAAACATCTATCA
GCTGGTGAATGGGTAAGTAAAATATGATATATCCATACGATGAATTCTTCAGCCATGAAAAGGAATGAAG
TTCTGATGCATGCTGCAACATGGATGATCCTGATGCTAAGTGAAAGAAGTCAGACACAAATGTCACATAC
TGTATGATTCCCATTTATATGAAATATCCAGAAAAGGCAAATCCATAGAGGCAGATAGTAGATTAGTGGT
TGCCAGGGACTGAGAGTAGGGGAGAAGGGGGAGTGGCTGCTAATGAGTCACCAGGCAATGAAAATTGTTC
TGAAATTAGATAGTGGGGATGGCTGCACAACTCTGAATATGATAAAAACCTCAGGAAGGACATCGAAACC
AAGAAAGGTAGAGGACAGTAAATTATAGCACTCAGTTCTATAGAAGAGGGTCAGCATTTACATTTCTAAG
GTTTCAATATAGGTGACACAGTTCTGTGCTACTTCCTGACTCACCTTGGTAATATTTACTGTGGCCCTAG
AGAAGCTGAATGGCAGTGCCTGTGAACATCAGGTTTGCCAGAGGAGAGGGAAGAGAGATGCAGACCTACT
ACCTGGAAGTAGCAACAACACAAAGGAAAAAGAGCATGAGCACACCAGAAGGCCAGGCAGCAGAACTCAG
GAGAAGCTAACTGCAGAGCCCTAGCAACACAACACAAGCACTCCAGGCACAGGGCCAGAACTGCTATTTG
TAATGGGGACTGGGATTCACTGAGGAAAAGGTATATAGTGTTCCTGGTATTTTACTTACTAAGGCTGAGA
AGTGGACAACATGAAGATGGATTTGATTTTTGGCAATAGTCCCAATGTCATTCAAAATTAAGTCTTGGCC
AGGCACAGCAGCTCACGTCTGTAATCCCAGCACTTTGGGAAGCCAAGGTAGGAAGATCATTTGAGGCCAG
GAGTTCGGGATTAGCCTGGGCAACATAGAAATTGTAAAAAATTAGTCAGGAACAATGGTGTGTGCCTGTA
GTCTCAGCTACTCAGGAGGCTGAGGTGGGAGGATCACCTGAGCCCAAGAGTTCAGAGTTACAGTAAGCAA
GGATCATGCCACTGCACTCCAGCCAGGATGACAGAGCATGACCTTGTCTCTTAAAAAAAGAAAAATTAAG
TCTCAAATTAGCCCTAAATTATCATTCGAATAAATGACTAAGAAGGGTACCACTGCTAACCATGTTCTGG
GTAGATGGACCATTGACTATAAGCAATTACAAAAAAGCAGTAGTGGCAGCAGTGGCAGCCACAGCCAGTG
TTTACTGAGTGTTTCATATTGTTGGAAGTGCTTTTATACACATCCCCTCATTTCACTCATAATAAACCCA
AGAAAAGGCACTATAATTATTCTCATTTTACAGACAAGAAGGACAAGGCTCAGAAAAGTGCAGTGACTGC
CTGGAGCGCACACAACTGGGAGACGACAGAAGCTGAATAAGAACCCAAGCAGTCTCGCTCCAGAGCCTGC
AACTTCAACCACTCCACACAGTGAGCTCTCTGAGAAACCTCCAGATTGTTGCAATAAGGGCTACAGACCT
CTTGAAGTAATATTTTCCTCCAGCATTTATTAAGAAAAAGTTCAAACAAATGGCAAAGTTGAAAGAGATT
GACAGTGAACACCCATATCCCCACCACCTGGATGCTTACTAAGGTGGCTGTTTTTAGCAACATTACCCAT
TTAGGTAAGCTTGGGTTTATTTGTTATGTATTTTTAAAGGGGTTAAAAATGGTGCTTAAACAGCAAAGTT
CTAATTATCTAGAAAATCATTCATCCAAAAGACACTCATGGAGCATGTCTGATAAATGAGGCACTACCAT
GTGGAAACATGCTATTGTCTAAGTCAAGCCCTAGTGAAGTGAGCTGATAGAAATGTAAGGTGCGGCCAAA
AGAGATTCAGAAGGAAAGGCCAGGTGATGTTTGCATTTTGTCATTTTTGTACAATCCTTTACATGCCCCA
TCTTGAAACCTTCTGCCTTGTAAATGGATCTTTAAATGGGGCCAGAGCAGTGGCTCACACCTATAATCCC
AGCACTTGGAAGGCCGAAACGAGTGGATCACTTGAGGTCAGGAGTTTGAGACCAGCCTGGCCAACAACAT
GGTGAAACCCCGTCTCTACTAAAAACACAATAAATTAGCCAGGTGTGGTGATGTGTGGCTATAATCCCAG
CTATCGGGAAGCTGAGGCAGGAGAATCACTTGAACCCAGGAGGCAGAGATTGCAGTGAGCCAAGATCGCA
CCACTGCACTCCAGCCTGGGACACAGAGTAAGGCTCCGTCTCAAAAAATAAATAAATACAAATAAAAATA
AAAATAAATAAATGGAAAAATAAAAACAAAAGTGCATAACTTTTTTTAAAAATCTGTCTTTGGGAATTGG
TAATTGCTCAATTCACTAAATTAGCAAAGCTATAGTTAATAGCCACTATATTTCAGCACTGCAGTATACA
TATGTGAGTTTTTTAGATAAAAATCTTAAAGTGTTTATCTTTAAATTATAGACTGAATTAGGAACTTTAA

FIGURE 1 (continued)

AAAATTCTGAGGAATGAATTGGAAGAACAGTAAGAATTCAATGAAGGAATTCAAATACTTAGAAAGTAAC
TCTTGACAGACTCTTCCAAGCGTTATGATAGTCAGCCTGCAGCCCTCTTGAACATATCACCCAGTATTTA
TCATTAAAAACGGAAATAGGCCAGGCGCGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCAAGG
AGGGTGGATCACAAGGTCAGGAGATCGAGACCATCCTGGCTAACACGGTGAAACCACGTCTCTACTAAAA
AAAAAAAAAAAAAAAAAAATACAAAAAAATTAGCTGGGCATTATGGCGGGCGCCTGTAGTCCCAGCCACTC
AGGAGGCTGAGGCAGGAGAATGGAGTGAACCCAGGAGGCGGAGCTTGCAGTGAGCAGAGATGGCGCCACT
GCACTCCAGCCTGGGCGACAGAGCGAGACTGTCCAAAAAAAAAAAAAAAAGGAAATAATGGTAGAAGTTGA
CAGAATTACAGAAACATAACTATAGTGGGAGATTTTAAGATAATATTCTAAAGATCAAGTGGACAAAGAA
AAAAGATGTAAAGAATGTGACTACTATGAGGTTGATCTGACAGACATGAATATAGTCTTGAGTATTCTAT
AGTAATTGACTTCACATTCTACACCATGAAACACATTTAAAAGTTACTCGTGATGTATAACAGACCATAA
ATAAACCTCAACCCATTCCAAAATAAAAATTCATAGGTAGCATTCCACTATTTAGTGCTAGCAACAAAGA
CTTACTTTGAAATTTATCCTTTTTACTTTGTTTCAAATTATGCTCTAAGTGGAAATTTCTCTCTCGGAAA
GAAAGAAAAGTGAAAATCCTTCCTATTCACCCCCAGAGATAAACCATTGTTAACAGTGCAGTATATATGA
TTTCAGGCATGTTTCCTAGGCATAGCTTACTATAATTAATTCTTTTAAAAAACCAAAAATGGAATTGTAT
TTTTACATCCTATTTTGACCCTGAGTTTTCGTCTCACAATTATTTAATTTCAATATCTTTCCATGTCACC
ATCTCTAGTTTACCTCAGTCTTTTAAACAACTTCAGCATTCTAGGTTATGGATGCATCATAGTTTATTTA
ACCATTCTCCTGATAAGAGACATTTGCATTTCTCCAGGTTTTTAACTATTACAATGACTCGGTGACCATC
CCTGCACATATTTTTATACATTTGAGAATTTCTGAAATACTGAATTTCTTACAAGTAAAATTGCAGTAGC
ATTTAAAATATTGTTAGCAAAATACAAAATTGTCTTTCAAGTAAACTGTACTGATTTTCGCTGTTACCAC
CAAAGAACTGAGGATGCACTCACTATCACTGCATATTCTTGCTATTTTCAGTCTTTGTTAATTTGATATA
TAAAACACTAATTACTAGTATTTGGAATCTACATTTCTTTATGAGCAAGGCTGAATATCTTTTCACATGT
CATTGACGATTTTGTATAAAATTATCTTTTGTCCATTTTCCTATGGGATGTCAAGTGTTCTCCATATATT
AAGAAAATGGGCTATTCTTTACCTGTCATAGATGAAACTGGGGTTTCATCTCCATTTTTTGGAGCCCATC
TACCACAGGAGGCAGTAAATGACATTAAAGAATTACTGTTAATGTTGCTATGTATGATAATGGTATTTCA
GTTATGTTACAAACAAAAGTCTTAATCAGTTGGTGATGCACACTCGAATATTTATGGGTAAAATAATTTG
TTATATAGGATTTACTGGGAGGAAAAACCCAACCCCCTAGAAAAAAATGAGGGATGGGTAGAAATACATG
AAATAAATTTGACCATGAACTTATAATTGTTCAAGTTGGGTTGGGATATATATGGCTCATATATATGCTC
TTATGTACATTTGACATTTTCATAATTAAAAAAAAATTAAAAGCTCGAGACATATTTTAAAAAGAAATCT
TGTATCATAAATGAAGCTTAAATTTATATTTTTAAAAAACATTCTGTTTTAAATGTTTCTCTCTTCCCTT
CCTTTGGAAAATGCTGACCTTGGAAACAAAAATCAGATGCAGCCACCCACCCTACTGCTGCCCAAGCCAA
TCCTAAGTAAATCAGTTGGCTTGCTGGGAAGTTTCCATGACCGAAAAGAAAACAGAATTCACTTCAATTT
CATCATCAAAGTCCACGAAAGCTTGCAAAGCACTTCCATATCCTTCTCAATCCATCCTCATAGTCTCCTG
AATTGGTTATTATTGGCCTTCCCTCATTGTAGTATTGAGGAGCTATCGAGCAAGAAAGGGGAGGTGATAT
GACCAGTCACACACGACATATTTTTGGCAGAGCCAGATATTCTGATTCTAAATTCAGTGTTCTCTTTTAG
ACTATATTCATTCTGAATACCAACTAAACAATACATCCACTACCTGTAACTATTTTGACATTTTTTTCTT
ACAGAGGGTTCGAAGATTTTACAACCTGAACTATTCTAGTGTTTTGTTTTGTTCTTTAAAAAGGCTTGAC
AATGTAGTCCTAGCTACTTGGGAGGCTGAGATGGGAGGATCTCATGAGCCCAGGAGTTTGAGGCTGAAGT
GAGAGCTATGGTTCCGTCATTGCATTCCAGTAATGTGGGCAACAGAGCAAGACCCTGTCTCCTAAAAATG
AAAAAAGAGGCTGGACCAGTGGCTCATACCTGCAATCCCAGCACTTTGGGAGGCCAAGGAGACAGGATTG
CCTGAGCCCAGGAGTTTGAGAACAGCCTGGGCAACATAAGGAGACTCCGTCTCTACAAAAAATTTAAAAA
ATAGCTGGCATGGTGACACGCATGCTTGTAGTCACAGCTAATTGGGAAGCTGAGGCGGATGACTGCTTAA
GCCTGGGAGGTCGTAGCTGCAGTGAGTTGGGATTATGCTACTGCACTTTAGCCTGGGCAACAGAGCAAGA
CCCTGTCTCTAAATAAATAAATAAATAAATAAATAAATGGTAAAAAGGCTTGACAGTTATTATGATCCTT
AGTATTTATAACACTTTTATACCGTCAGAAGAGGGTCTGTATTGCTTACTCTTATGTATTAATAGAGAAC
TCTTTTAACATGAGGCTTGGTGATTAGACCACGGTAAGTCAGTAGGACTCTATAACAAAAAGAACATGTG
GAAAACTGTCCTTCCTCAGGAATGTGTGTGGGCAGGACCTTGGCAGTCCAGTAAGTGGATGTGCTGGTTG
CAATTGTCAGATTTCTGCTGAAAACAAAAAAGTTACAAAGAACTCAAGTCTAAATCCTCAAATGTCAAAG
CAATGTCAAGCCCAGAGCTGGCCTCAATTTGCCCTCTGGTTACTTAAGGGTCACAATAATTTCTGCATTT
AGTAATCACCATCAGCCAAGGGCTCAAGGCTAGAGCTCTCTACTTGTTTTTCCCCCTCAAACAGTGCTGT
TTTTTTTTTTTTTTTTTTTTTTTTGAGACGGAGTCTCGCTCTGTCGCCTAGGCTGGAGTGCAGTGGCGCGA
TCTCGGCTCACTGCAAGCTCCACCTCCCGGGTTCACGCCACTCTCCTGCCTCAGCCTCCCAAGTAGCTGG

FIGURE 1 (continued)

GACTACATGTGTCTGCCACCACGCCCAGCTAATTTTTTGTATTTTTATTAGAGACGGGTTTTCACCGTGT
TAGCGAGCATGGTCTCGATCTCCTGACCTCGTGATCCACACGCCTCCGCCTCCCAAAGTGCTGGGATTAC
AAGCGTCAGCCACCGCACCTGGCCTTCCCCCTCAACTCTTATTTTTGTCTAATCACCAACAGAAATAGCC
CACTCTAGTCAGATATTATCACCTCTAAAGTAAACATTAATTTGTTCTTTCTCAAGCTCAGAAGGTGATT
GTGATATAAATACAAAGGCCTCAGAATTAAAGAGACTTTAGAGATCATATATTCTAACCACTCACCTTTG
CATGAATTTTACCTTAAGTACCACTACCAGGTGGTTAGGATGGCCTATACCTGAAGATCTCCAAAGATAG
GGAGCTTGGCACTTATTGACACTAGAAAGATGTTTGAAATGGTTCCTTGTAGTAAGCACCAAAAACAACA
AAACCTTCCTATAAGTTTTATTTGCTAAATTTGTTTTTTCTCTCAAATAGAGTTGAGGACTTACTATGTG
CTAGGCACTGGGTATACAAGGATTTTTGAAAAGATGCTAGCTAGCCCTATAACTCAAGAAGCTAACAGTC
TGTTGTGGTTATTAAGCTATCCACCAGGGCTCTGGGCCTTGCCCTCCACTGGATGCATTGAATTTCCCTG
CCTACCTGAAGTTAGGTGAAACCAATGAAACGTGAACAAATGTGTCACCTCCAGGGGAAAAGTTTTATGA
GAAAGTATAGGCTTTGCCTCACTATTTATTCTCTGGCCTGCAACTGGTTATGTTCCAGATGGCGGCTACT
CTATCAGCCTGAGTCCTAAAAGAAGAACAATAGCTGACCTGCCATGTACATGCAGTATGAACAAGAAATA
ACCTTTGTCACTTTAAGCTACTGAGGTTTTTGGAGTAGCTTGTTACTGCAGCCCATCCTCACTGATACAG
AGTCTGAAGACAGACAAACAAAATCATCAGCAAAATGATCAACAAAGTCATCAACAAAATGATCAACACC
AATCAGACAATAAGCTGAGTGTTGTAGTGGAAGCATGCACAAAGTTCTGTGGAGCATAGGAAAAGACTTT
CTACCCACCTCTGTCTTCCGGGGAACTTGGGGTAAGGCCTCATAGAGGAGGTTGCTTTTGGATTAGAGCT
CGAAGGATGAATAAATACTGCCAAGTAGATAAGTTGAGAAAAGAGTGTTCTAGACAAAGGGAACACTTTA
TACAAAAACCGTAGAGGGAGGAGAAAACATGGCATGATTGGAGAGCTAGAAAGGATTCAGTTTTGCTATT
GTACAAATCTGAATGTGGTAGATTTCCTATGAAGCTACTACAGCCGAAGCTTTGGGGACCCTCACTTCAC
TTGCACAGGCACCTTCCAAAGCCTCTATCTAACTTTATATCTTTATAATTTTATTCTTAGATTTTTTTCT
TAGGAGGGTCCCCTTTACTAATGTTCAAGTTCCACAAAAGCTGGATCTGCTTGTGATGGATCAGGTTGCA
GGAATAGGAGGTGATTCTAGGTATACAAACAAGATATTTGACTTTCTATATGATACAGTTTTTTTTGGTT
TTTTTTGTTTTGTTTTGTTTTTGTTTTGTTTTGTTTTGAGGCAGAGTCTTACTCTATCACCCAGGCTGGA
GTGCAGTGGTACAATCACGGCTCTCTGCAGCCTCGACCTCCCAGACTCAAGTGATCCTCCCGCTTCAGCC
TCCCAAGTAGCCAGTATTACAGATGCGTGCCACCATGCCCAGCTATTTTTTTTTTGTAGAGATGAGGTTT
CGCCATGTTGCCCAGGCTGATCTTGAACTCCTGGACTCAAGTGACCCACCCGCCTTAGCCTCCCAAAGTG
CTGGGATTACAGGCATAGCCACTGTGCCCAGCCGACACATTTTTCAATTGGAAAAACGTGATTTTTTGGA
AAAAAAGAATCATGTTCCCTAAAAGTCTTCTTTTCCCCTAAACCAATAATCCTCAGTTCCTGTACTTTGT
GTGACTGGGACAGAGACTCCACACCACTCTCCACTGTTCTTCTCTGAATGTGCTCTTATTTGTCTATAGC
CTTCTCAACAGTGGCATCTAAATCTAAATCTAATTCTCCAGATGTAGTCTGAGCGTATTTATCACCTTCC
TTAAACTTACTCATGTCATATTTAATCTTTCACAAAAGTTTTTACCCAAACGATGCCACATTATTTATAA
TGTGAGATTCCCCTGAAAAATATGGATCAATGCTCTTGGATTTAATCCACAGCACCAGGACTTGTACCAA
AATACAATACCTGCTTGTTTCAATTTAGGTTTGGCAGAATTTGAGGAACAAGTTTGCAGAGAAAAGATAG
TCAATTCATTTAACAAATGTTTACTAAATGCCTTTTCTATGCCAGACATGCCAGAATATGGGGAAGACAA
AAAAAAATAGATAGAAATCTCTGCCTTCCTGGAATTTACATTCTAGTTTGGGGGAGAGAGATAATAAATA
AAATAAGAAAATGAAATTATGTGTCAGAGCAAAAAGTGGAAGAAAAGCATAGCAGTGAAAGGCTGAAGAA
ATGTGGAGCATGGCAGGGGTGAGACTGCAATTTAGATATACAGTGGTCAGAAGAGAACTCACTGAGAATG
TGACACTGGAGCCAATACTCAGAGGTGTGGAAGTGAGCCATCTGGGTAAGTGAGGAAGCACACTCCAGGC
ACAGGCATCAGCTGGTGCAAAGACCTTGAGGTGAGAATGTGCCTGACATGTTCAAAGAACAGCAAGGAGG
CCAGCAGAGCTGGGCGGCGGTAGTAGAGAGACAGTAGTATGAGACAAGGTCAAAGAGGCTGTGGTAGGGG
GCAGGGAGGGGATCCATGCAGGTCCACTGCCATGATCTGAGTCTCTCTGAAATGGGCAGTGCCAAGAGAG
GGCTTTGAGCAGAAGGTTGGCGTCATCCGACACGTGTCCTTCAGCATGGCTCTGCTGGCTATGTTGAGAA
CAGACTGTAGGAAAACACAGTGGAGAAGTAGGGAAACTTGTCAGACATCAATCTAGGCAGGAGATGACAG
CAGCATGGACCAGGATGGTAGAGATGGAGGTAAGAAGAAGTGGCTGGATTCTGGATATGTTTTGAAAGTA
AAGCCGAAAAGACTTCCTAAAGGAATGGATAGGAGGATGTGAACATTGTAGCCACGGGAATCAAGGATGA
CTCCAAGATTTTTGATCTAAGCAACTAGAAGGATAGTGTTGCCATCAACCAAGATAGGTTTAAACCTGGG
AAGCTTTGTGAAAAAAGCAAAGCAAATCTGTGCTGCTAAAACTAGAAGGTCCTTTTCCAGGGGAAAAACT
GGATTGAACTGGTTTGGTCACAAGTGTTGTAGGAAATTAATGGGTCAGACTGCTAATGAGCAAAGAGGCT
GTGTAGTGCCAATGTTCCCAATGAAAAGACTCTGGTCTTTGCCAAAAGCTGCTCAAATCTACAGAGAAAC
TACAGAAATGGGGGTTGGGGGGAGGCTGGGACCAAATCTAGGGTATTATAAGAGCCAAGTAGTTAGAAAT

FIGURE 1 (continued)

TGCACTCTCTGAGGTGTGAGACAGCGCCTTTCAAAGTTAAACATGTTACTTTAAATGTACTTGCATCCTA
AATGTTGTTCCAAGTACTAAGTAAATTACTTTATTAAATTTAAAACTAAACAGTAAAAAAGAAATTGTTC
TGGATGTGGTTTTACTTCTGAGATTACATTTGTTTTGTTTTAATTGAAATTTTCCAGTGTGGGCCAGATA
GTTTACAGGCTGAATAGCTTGCAGGCTGGTGAGCTCACTTGAATTTCTCAAGAACATTTGTTAAAAAAAA
AAAAAAAAGAAAGAAAGAAAGAAAAATTCTCTCTGGCTGACCACTGTGGATAAGATGTTCCTTTTACCTC
TTCCAGGCTTAGTCTGTATTGATGATTTTCTTCAATGGCCTCACTACAAAGTCCAGCAAGATCTTACACA
CAAGAAAAAATGCTCAATTTCACTCACAGTAAGAGAAATACAAATTAAAATTACTCTGATTATTTTTCTT
TCACTTACTTTGGAAAGGCTTGAAACATTGGATAATAATATCCTGAGTTGGCAAGGGTTTGCAGAAATAG
GCACTCTCATACACTGCTTGCTGGAGTGAAAATTGGTAAGACTTCTATTAAGAAGTATTTAACAAGAACA
AAATTATAAAAGCTCATTCCCTGACTCACCAGATTCTGCCTCTAGGAAGGCAGCCTGCTGATATACTTTG
CACAATGGTAAGTCATACATGTATAAGGTAATCTACTATCAGCATGGTAATGGCAAAGGACTGGAAATAA
CCTAATCACTCATCAACAGGAGATAATCAAATCAATTATGGCACACTTATACAATGGAGTAACACACTTG
TGAAAAAGAACAAGGGAGGTGCTTTTTATGCTGCTATGGATTAACCTTCAAGCTATCTTGATATATGTTA
AGTTTTTTAAAAAGCAAAGCACAGAATAAAAATTATACGCTAGAAATACCTCGAGAAAAATATGTGAGAA
ACTAATAATAGTGTTTGCCCCTGGCGAGGGGAAGAGGGAGATGTGTTTGAGGGAAGCTTTTCCCTGTAGC
CCCTTTTAAATTCTGAACAATGTTAATGTGCTATGTATTCAAAACAAAAAGTTAAAAATTGAATAAATAC
ATAAGTGGAAAAAATGTTAGCATATTTCCCAAAATACATGGGTTGTTACAAATAACAAGTGAGAAAGTGA
GAAGCTAATGGCGTCAGAGTAGAGGTCCTTACAGAGTATGTAACTGGGTCAAATACCAAGTAGTGCTCCT
TTACATTTCAAACTTCTAATAGCTACAGATGAGCTTTTGGTGTAACTTCTGTAGGGGTGCATGTGAGCAC
TTCACTTAAAACTATATATTATATATTGCATTTGCCTCTGGCCATAAAGCCATAGTTCAAAAATAACTTA
GAGATATCCAATATACAAAACAAAAAATAAATAAATAAAAGAACAAGCAAAACAAAAAAAATACCCAAAA
TGGAGGAGTGGGACAATATATGCAGTCCAACTTCTTTCCTAATTAAAAAATCCTGCAGCAATCTGTTATC
CAGTCTCCAACTGAGTATCTCCCAAATGTGGGAGCTAATTATCATTTATGACAATTTATTACAAAGCCCC
TTTCTTAGTTGGACCTGGTTCCCAGCTTTTAGATTTGTCTTTTGGACATAAATCAACTCTTTTTACTACA
TGACGCATCAACTCTCTTTTCTATATATCAGCTTTTCACACAGTTGAAGATCATTTCCTCTTTTAGTATT
TACTTCTGCAGCTAAGTGTCCTGAATTCATTGCACATTCTCTCTATACATTCTAATTTGTCTGCATTTCT
CACAAAATGTGGCAATTAGAACTGAACAAAGCATTCAAGATGTAGCCCAACCAGAAGAGAATTAAATGGA
AGCTGTGTTTTCATCATCCTATTACCATGACTAATACAACCAAAAACTGAGCTAGATACAAGTTCTATTC
TCCCCCTCACAGAGGAGGACTTTGAGGTGAAGTGACCCAGTGGGACAAGGAAACACTGCTAGAATTAAGG
AGGATTAGGATTCTTTCATCACAAGGCCATTTGGATACACGTTTTCAGACACTCATTTATAATTCCAACA
GAGGACTTCTGAGCTATCTTCCCCTTTGCCTCTTTGAAATCTACCTTCTTAAGAAAGGAATGTTAGACTT
TCTCTGAACATCCTATCTAAATGTCTTTGGGGGCTCCCCCAAATCCAAGCTGAATTATTCTCTATCACAG
CATCCTAATTGTTTCTTTCATAACATTTATCAAAATTTGTCTGGATCTTCATCTGATTCTTTTCCTGCTT
ATTGTCTTTCACTTTGGCTAGGCTGTAAGCTCTGTAAGTAAGGTCAGGGCCTATATCCACTGTTTCCGTA
GCATATAGCACAATGTCTGGCACATAATAATCGTTTTCAGTGAGTGAATGGGTGAATAAACGGTAGCTGA
TAATGGAGTTAAGACTCTAACATCAGACAGAGCCCTAACACTGTGGACTGTGTATTCCTGGGCAAATGAC
TTAAGTCCTCACAATCCATTTCCTCATTGGTAAAATGAGGAGCTATTAATACCTACCTCATAGACCTGAC
ATGACATTCGGTGAATTGATAGGAAGTACACAAAATGATTTAGCATGCTGTCTGATATACAGGAAACACT
CAATAAATCATAGTTACTGCAGCTACTGCTACTGTTCTAATTACCACCACATCCCACTCAGAGGCTGGCC
ACTGAAGGATGACAATTAACTGTAACAGCTAGAGGTACATCAGCTGTTTTACCCAGCCTACCTTTCTTTC
TTTTTAAAAAATTGTGATAAAAAACACATAACATAAAATTCATTGTCTTAACCATTTGTTTTTTTCTTTT
GAGATGGAGTCTCACTCTTGTCGCTCAGGTTGGAGTACAGTGGCGTGATCTTGACTCACTGCAATCTCCG
CCTCCCAGGTTCAAGCGATTCTCCTACCTCAGCCTCCTGAGTAGCTGGGATTATAGGCACCTACCACCAC
GCAGGGCTAATTTTTGTACTTTTAGTAGAGACAGGGTTTCGCCATGTTGGCCAGGCTGGTCTCGAACTCC
TGACCTCAGGTGATCAGCCTGCCTTGGCCTCCCAAAGTGCTGGGATTACAGGCGTGAACCACCGCACCCA
GACTGTCTTAACCATTTTTAAGTGTACAGTAAGGTAGTGTTAAGCACATTCACATTGTTGACCAACAGAT
GCCCAGAACTTTTTAATCTTGCAAAAGATGCAAATACTATACCCATCAAATAACTATTCCCCTTACTCTC
TTCCCCCAGCCCCTGGCAACTACCATACTACTTTCTAAGAGTTTGACTACTTTAGTTACCTCATATAAAT
GAAGTTATATTTCAAGATGTAGCCCAACTAGAAGAGAATGAAAAGCAAGCTGTTTTCATCATCCTACTAC
CACTACTAATACTACCAGAAACCTAGCTAGCTAAAAAAAGTACTTATCTTGGGCTGGGCGCGGTGGCTCA
CACCTGTAATCCCAGCACTTTGGGAGGCCGAGGCGGGTGGATCATGAGGTCAGGAGATCGAAACCATTTT

FIGURE 1 (continued)

GGCTAACATGGTGAAACCCCATCTCTACTAAAAATACAAAAAATTAGCCGGGCGTGCTGGCGAATGGCAT
GAACGCGGGAGGTGGAGGTTGCAGTAAACTGAGATCGCGCCACTGAACTCCAGCCTGGGTGACAGGGCAA
TACTCTATTTCAAAAACAAAAGAATTTCCTTTCATTTTAAGGCTAAGTAATATTCCATGATATGTATATA
TCATATTTTATTTATCCATTCATCCACTGATGGACATTTAGGTTGCTTCCCCCTCTTGGTTATTGTGAAT
AATGCTGCAGTGAATATGGGTGTGCAAATATCTCTTTGGGATCTTATTTTTTATTCTTTTGGGTATACAC
TTTTTCTTGTTTAAGCTCTCCACAATCCTATGATGCTGGCAGAGCAGCAGAAATCACAGGAGTCATCAAT
TCGTCTTTACCTTTTTTGATCCTGTCATCAAATTATCTTCCTCTCAAGCTCACTCCCTAGTCCTTTCTGA
TAACCTCCTGGTTCCTCTATTTTCAAGTGAATTCAACAGGTCAAATTTAAAATTTATTTTACTTGTCCAA
AAGGGAAGGAAGCTATTATACCTTTCCTATCCCTTTCTGTTGGAAGAACTCTAGGTTCCTCATCCAGAGA
AGGGTACTGCCCCAGGTCTGAGCAGAATGAAGCTGCAGGTACTCAGGGTCTAAGCCCCCTGGAACAATAG
AGGGCTATGGCTCTACCTTAGTCGGCCCAGGACAGTTTCTAAAATGTTTCCTTTATGAGTACTGTTTTGA
ATGCTGTTAATATTTCATCAGGAAGTATCAGTTTCCCTTGACAGGTAAGATTAAGTCCTATTCACTGGGT
TGATCAGCCTTATCATTACAGCCAGGATATTTCTCTGCAAATCCCCTTCCAATCTTATGCTGCCCAACTA
ATGGGACCAACTGGATTTGCTCAATAAAGTTCTGTATTTTCCCAGAGCTCTTCATTTTCACATTATTGTC
CTGGGGTGGGGGGCAGCAGAACAGAGATGTTGACAGCCAAATGGAAGATGCATTGGGAGGCTTCTGAAGA
TACTTGTTCTGTCTTTGAGAAACCTTAGAGCATCAAGGTGAAGCAAAAGGAAAGGAGAGGAATAGTGCTC
AGTACCTGAGCCTTCTCTAATCTAAAACGCAATAAAGTCAATCATAAATCCTGAAAATGAGAGTGGCTGT
GATGGTGCAAAATATAAAACTCCAACAACTATTTATCAGGAATGAAGTACATATATCTCCCTATTCGCAT
CTCAGCCTTCCTCCTGCAATATGTGAGTGAGTGTGCATGAACCCACACTCACCAGTGATACACTCAGGAG
AGTACTGGGGAAGAGTTAACTTCCGCTGCAAGATAGTTAGCATATTTATTTCCTTTCCATGAGACTTCAG
GAGCCTAAATCAGAAGTTTCTAAGAGCTTCTCTTGATGTCATATATTCTGAGAATGGATACATCTAAGAA
CTGATGTAATGTGTCTGCCATTATGAATTTGGTAAAAGTTCTATTTATCTGTTTTTAAACAAAAGGACTG
CTTTAATGTTACATATTGGTTTGTTATTACATATTGGCTGGTTATTTGTTATTGGTTGTTTCTATGACAC
ACTTGGACAAGAAAATTTCTAGTCCAAGTATATCATAGTGGTATTACTTGAGACACCACTTAAATCTCAT
AAAAATAGAAAAGATCCCCTAACTGGCCTCTCCCATCTTCCCCCTCCCCCATGCCAGACTGCCTCTGTCC
CACTTATTCAACTTCCTTGCTCATCAATCTTTGGTGCATTGCAGGCCCCATTCCTTCCTCTCCTTCTGCC
CAAACCACTTGCACCAAGGTCATCAGTCAAGTGGCTCTTTCCTACTCCTTCAAGTCTCAAACCACTCAGG
ACCCAAAGGAAGTTAAGACCCACACCTCTATAACCTCTCCAAAGGGAGCAAACTCATGCCCAGGACTTTG
CAATCTCCTCTACCCAAGAGATTTCCAAATCACCCTTGCCAGCCCTGACCTATCTACCAAGTTCCAAATC
CATTACTTCCAACTGCCATTGATCCCTGCAGGTTTTAAAAAACTACATGCATAAATTTCTGGCTCCGTTG
ACCCTGGCACTCACCCTTCCAAAAAACGAAACAAGCAAATAAAAAATATAGCCTAGGTCTACTTCCTAAA
TCTTCATTTCACCTCTCACCATTTGTCTTAGTCCGTTCGGGGTGCTATAACAAAAACATCATAGACTGGA
TGGCTTATAAACAACAGAAATGTATTTCTCACAGTTCTTGAGGCCAGGAAGTCCAAGATGAAGGTGCTGG
CATATTCAGTGTCTGGTGAGGGCCTACTTCCTCATAGACAGACAACTTCCCACTGTCCTCACATGGCAGA
AGGGACCAGGGAGTGTCTGGGGTCTCTTTTATAAGGCCACTAGTTCCATTCATGAGAGCTCTATCCCAGT
GACCTAATTACCCTCCAAATGCCTCACCTCCTAAGACAATCACATTAGGGATTAAAATTTCAACACGTGA
ATTTTAGGAGATACATTCAGTCCACTGCACCATACATCCAGATTTCCAAGCATACTTATTTTTTTCCTAG
TTTCCTTTATTCACATCTCTCTTTTCTCTTTTCCCACATGAAATGTTAATGGTCTCGGAAGCACTTAACA
TCTTTTCTTGGTAGAGGGACTTTTAGAAATTGTGGTAAAATACACATAACATAAAATTTACCATCTTAAT
CATTTTTAGGTGGAGAGTTCAGTAGCATTAAGTATTAACACAGTCACATTGTTGTACAACCATCATCACC
ATCTGCCTCCAGAACTCTTTGCCTTATAAAACTGAAACCTTACACCCATTAAACAATAACTCCCATTTCC
TGCCCACCCCTGACTCCTGACAACTACCATTCTGCTTTCTGTCTCTGTAGATTTGGCTACTCTAGGTATT
TTACATAAGTGGACTCATATAGTATTTGCCTTTTTATAACTGATCAATTTAACTTAGCATAATATCCTCA
AGTTTCATCCATATTATATGTCAGGATTTACTTCCTTTTAAAGGCTGAATAATATCCCCCTGTATGTATA
TACAACATTTTATCCATCTATCAATGAACACTTGGGTTGCTTCTACCTTTTGCCTATTATGAATAATGTT
GCTATGAACATGGACATACAATCTCTTTGAGTCCCTACTATCAACTCTTCTGGGTAACTACCCAGAAGTG
GAATTGCTTAATCACATGGTGATTCTATTTTTAATTTCTTGAGGAATTGCCATACTGTTTTCCATAACAG
CTGCACCATTTTACATTCCCACCAACAGTGCACTGAGTTCCCAAGAGTTCTCCACATTCATGGCAATATC
TGTTATTTTCTTTTTTTTTCTTCAGAGTTGCCATCCTAATGGGTGTGAGGCTGTATCTCACTGTGGTTTT
GATTTGTATTGCCTAATTATATTAACGTTGAGTATTTTTAATGTGCTTATTCATTTGTGTATCTTCTTTG
AATAAATGTCTATTCAAGTCCTTTGACCATTTTAATCAGGTTGTCTGGGGTTTTTTGCTGTTTTTGTTGG

FIGURE 1 (continued)

GTTGTAGAAATTCTCTATATGTTCTAGATATTACCCCTTTATTAGATATATGGTTTGCAAGTGTCATGAA
GCTTTTCTCCTCTGTCTTCTTCTAAGCATTTTATAGTTTTAGATCTTTTGTTTAGGTCTTCGATTCATTT
TGAGTTAACTTTTATATATATGGTGTAAGGTAAGGATCCAACTCTATTATTTTCCATTAGATAGCCAGTT
TTCTCAGCACCATTTGTTGAAAAGACTGTCCTATTCCCATTGAAAGGTCTTGGCATCCTTGTAAAAAATC
ATTTGACCTTATGTGTGAGGATTTGTTTCTGGTCTCTCCATTCTACTCCATTGGTCTATATGCCTTCATT
AACAATTTTTAATATTAAATAGATGTTGAAATAATATTTTGCATATATTGGGTTAAATATATTCTTAGAT
TTTTTTTTTTTACTGTTTCAATGTGGCCCATAGGACACTTATCACGTATTGGCTCTCATTGTATTTCTGT
TGGACAGCACTGCCTAGATGCTTCAGACTGGAGCCACCGGGCAGTGTGGAGAGCAACAGCTAACGTCATG
GGATTAGATGATCATCTGAAAGCTCCTCTCCTCTTGTGTTTATCATTATAGTACTTAGGGAGCAGGATAT
CACTGTGGCTGAGAATTGAGGCTTCTGAGTCAGGCAAGTCCAGGTTTCAAGACCTGCCCTGTCCAACACA
GCAGCCACTAGCCATAGGTACTCATGTATGTACTGAGTATCTGAAATGTGGCTAATGTGAATTGAGATGT
ACTGTAAATGTAAAATACAGACCAGATTTCAAAGACTCAGTACCAAAAAAAGTAAAATATCTAGTTAATA
ACTTTTATATCAATTACATGTTAAAATATTAGTATTTCTGATAAATTGGGTTAAATAAAATGTATTATTA
AAATTAATTTGACTTGTGTTTCTTAGTAGGCTATTTTTTAGATCAAGTTCACAGCAAAACTGACCAGAAG
GTATAGATATTTCCCATATACCCACTGCCCCACACATGCATAGCCTACTCCATTATCAACATTCCCCACC
AGAATGGTACATTTGTTACAACTGATCAATCTACACTGACACATCATTATCACCCAAAGTCCACAGTTTA
CATTAGAGTTCACTCTTGGTGTACATTCTATGGGTTTGGACAAATTTATAATGATATGTATCTACAATAT
TATAATATCATACAAAATAGTTCTACTGCTCTAAAAATCTTCTGTGCTCTGCCTGTTCATCCCTCCCTCC
TCCCTAACTCCTGGCAACCACTGATCATTTACTGTCTCTATAGTTTTGCCTTTTTCAGAATGTCATATAG
TTGGAATCATACAGGTATGTAGCCTTTTTGGATTGGCTTCTTTCACTTAGTAATATGCATTTAATCTCCC
CCCATTGCTTTTTATTTTTTGACTTGTTAATTTTGATTTTTTAAAAATGTGGCTCCTAGAACATTTTAAA
TGACATATGCAGCTCACCTTATGTTTCTGCTGAACATTTCTCAGCTTGGCATGGGCAGTTTTTCTCAGCA
TGGCATCTTCCTGTCTTTCCAGTCACTCAAGTCCAAGCCTGGTTGTACTTGGTTTGCTGCAACCTAAACA
CACCAGCCTCCTTGCCTTCACACATACTAGAGTTCCTTCATTAGAGTTTTCTTTAACCCCCTCCCTCACC
TGAAGACTAATTCATGCTCAGACCCAATTCAAATACGACATCTTTAGTGAAGCCTTTCTAAACTTCCACT
GTACCTAAATCATTTTTTATAGCACATTCTACCTTATAATTTTTTTGTATGTGGCTGACTTTCTCTCCAG
ATTGTGAAATCTTTGAATTAGGCCCCATGTTTTGTTCATCTTTGGGTCCTCAATCCTTAGTACAGAGCCT
GACACATGGTAGGCAATCAGAGATGTTAAGTTAATAAATGAATAAAATGCAGGAAAATTAACATATCCTC
TAATAAGAGATAACATATTCACTTAGAATCAAATAGCTTAGAAAAGAACCTCAAATGCCATAAACAAGGG
TGTAAAATTCTATCAGCCAACAGCTAAAATTATTCACAAGCTAAAATTTGTATTCAGTCAAAGCAACACA
TTAATCAATAATATTTATAAAGTATATCACAGTGAAAAGATGGTAAAGCACCTCCTAATGGTTAATGATA
GTGATTGGCCTGGAGATGTGGAAACTAGCTATGGAAACTAGATGGTTAAAACAACCACATTCCGTACCAT
TAGACGCTGACAGCCCAGACCCCACCAAAATAGAGGCAGTGAAACAGCCTTTGAAGTTGTTTTGAAAGGA
AGCCACCAAGATGATTAAAGGGTTGGAAAATGAGATTTATGGGTAATGGCCACAGAAACGAAGACAATTT
TGCCTAGGCAAGAGAAAAGGCCGAAGGGTGACTTAATAACCATCTTCAATCATTGTTATTACACAGAGAA
TGATGACCAGATGGTCTCCATTTTCACCAGAGAAAGAATATTGAAAATGGACTTACGCTGCAGCATAAAA
AAAAAAAAAAGGTCTAGTTTTAAACAAAGAACTCAATGGTTAAGAACTAGTATACAGCAAAGCAGACCTG
GGGAGTGTGTGGTGTAGCCATGTCTGAACTCATCTGTTATGCTGGGAAAGCAGCAAGTGGGTAGGGTGTG
TTCAGGTCTTCAACAGTCCTTTGTTGAGGGCAAATTCTCAACTGGCTAGTCCTCAAATGAATCACGTAGC
ATACAACCACAGGAGTGGAAAAGAAAGAGATATGAAAATTGAAACACAGCACCCTCTGGTGTACATAGCT
GTCTTCTAATCTAGGAAAATTCTTCTTTTTTTTTTGAGACGGAGTCTCGCTGTCGCCCAGGCTGGAGTGC
AGTGGCGCAATCTCGGCTCATTGCAAGCTCCGCCTCCCGGGTTCACGCCATTCTCCTGCCTCAGCCTCCC
GCGGGGGACTACAGGCGCCCACCACCTCGCCCGGCTAATTTTTTGTATTTTTAGTAGAGACGGGGTTTCA
CCGTGTTAGCCAGGATAGTCTCGATCTCCTGACCTCGTGATCCCCCCGCCTCGGCCTCCCAAAGTGCTGG
GATTACAGGCATGAGCCACCACGCCCGGCTGGAAAATTCTTGATATGTATCAGTATTTTTCAAAATGTAA
GCTCCAAACCATGACAGAGTCAGGAGAAACTTACACAAGGCTGGTCTTAGGGTTCGTTTAATCGCTACAT
CCATCTTTATCAAGCACCTGCGATGCATTTCTCCCTGTTACCAGGAGGTACCAGGAAGCCTGTTACACAA
GCAACCTCAACTTCTGCCTATAGCAAACTTGGATTCTTCCCAATCACCTTTTGAATGCTGAATTCAGACT
CTGATACAACTAGCTGGCACATGACCATGCAATGCTGAGACATGATAACATCTGCCAGATAATGTGAATT
TTGCCCTGTGTTCAGGAGTACATTACATATAAAAGTTAAGCAACACCTAAATGGGGGTGTTCCCTTAGAC
ATTCTCCCTGCTATGTTGTGGTGTATACACCCTTCTTTACTGATCTCTGTCTGCCAAATCCCAGCCGGCC

FIGURE 1 (continued)

ACTTTTTACATCCTCCTAGGCTTTATGCTGCAAAACCTTCCTAATATCCTTTTAAGTACAAAAGACATTC
AATGAGCTCAAAAAGTTTGAGACCCAATCAAGAATCTTTTGCAGCCCTCTCAGTATCTTTAGCCATCTTG
TTGCCAGATGGGAACTTCATTCACATGACACACATACTTCCTTCATGTGACTCACCATTGCTAAGCAACT
GGTATGTCCTAGGTGAATAAAACATATGCCCTGTGTCTGAGATTCACAGTGCAGTAGGGGAACATGGATA
GATACGGGTGTAAATAGATCAGCTGAAGCATGAGTTGAAGCTCAAGGCTCTACATGCCAAGAACAGAGGA
AAAAGGCAATGGAGAGACCGGACAAGAACTATCAGGACATCAGAACAGAACTTACATCCTGTGAGAGCAG
GACTTATGCTAAAAACAAGTCTTAAAGGATGAAAAGAAGTTGTCCAGGCAGACAAGACAGGAATATGTAT
CATCCTAGGCATAAAGTCCCAAGACATGTCACCTTTTGAAGAATGGAGCCATGTGGCACACTGTCCTCCA
GTCCCAAAGGTCTCCTTGAAGAGACATGAAAATCCCACCTGAAGAACTCACCCTTGCAGATTGTACATAG
CACAGACCTAAATGGCAACAAACAAGCAAACAAAAAACGCAGTACAGACTAGGCACTGATCTGATGGAAG
CGAGACAGGCTGGAGTAGCAAAGGGTCTGACTAAGAAGCTTAGGAGGAATTCCTCTGATACCCTTCTTGG
TGCCCCCTCCCCAGCAACATCTAACAGCCTCACTCGGGCCCAACTTCCCTGTTGCACTGGTGGCACTGCA
TTGCAATTGTGGGTACAAGATTCCTCCCCCACAAAACTGTGGGCTGAGGCAAGAGTTCTACCTTTTTATT
ACTACGCCTCTGACACTCAGCACATATGAAGCACAAGCAAAATTTGATGACTAAGCTAAGTAATTAGTTC
ATATGTGTGATTAGGGTTTGAAAGGGCAGAACCTTGGACCTATGATCCCAAATACCTTTGTCTATCTAGT
TCACCTGGTTTTGTTCCTCCTCAGAAGCCATCTATCCTCCTTACCTTGGTTCATGTTTTCCTATCTCTCC
ATTTTATACACATAAACCAACTCCTACCCTCAAATCAGGGAAAAGGGACAGATATTCCTGTCCTCAAGTT
AAGAGTGACCTATGTCAAAGTGAAAAACAACTAAGCCAAAAAGGTAACAGGGAACTGGCTTCTTGAGCAC
TCAGAAGAATTTGAGATTACTGCCTCGCGAGGGAAAAAGGGAAACCCAACCCGATTACAGTGTAAAAATA
GGTCACTGCTTGAATACAGCCCTTTGGTTACTGGCTGCAAGCCCCTTTTTGCTTTTGACTCCAGTGTCAC
AAGAAAGTGGCAGCATAGTCTTAGAATAAGGGCTCCACAGCCAGCTGGCTGCTCGGCCAGGCCTTCCTGC
TGGCATTCTAGAAGCAGCATGCAGGGCCAGGCACCTACTGGGGAGCTCAGTAAGCCTTTGTCACTGCTGA
CATGAAATACAAGAGTTGGTAAGTTTCTTTGGTTTTGTTTTGAACAAACTGGCAGATAGTTCAAGGTTGT
CCTTGTAAGTCTCTCTCACTTGCATTCAGCTATACATTGTTTAGTAGGAAATGAGTATAGTTCAGCTAGT
TCACTTATCCCCATGCCAAACCAGCAGGCAGCCTCTTTTCCATGAGAGACAGTTATAATTTTGAATTATT
GTAATGCTGTACTTGCAGCAAACTCGGTGTGTGTGTGTGTATGTGCACACATGGCTGGGAGTGGGGGGTA
GTGCCAAAATGTTGGTTCTATGGCAAACAACAACAACAAAACAAACAAACAAAAAAACCGGCTGTGTATA
GCTAAAAAAACATGGCCAAGAAAAAGGTAGAATAGAAAACATGTTTTATTATCCTGATACTAAAGCCTGGC
AGAGACACAATAAAAAAAGAGAATTTTAGACCAATATCCCTGATGAACATCGATGCAAAAATCCTCAATA
AAATACTGGCAAACCGAATCCAGCAGCACATCAAAAAGCTTATCTACCATGACCAAGTTGGCTTCATACC
TAGGATGCAAGGCTGGTTCAACATATGCAAATCAATAAATGTAATCCATCATATAAACAGAACCAAAGAC
AAAAACCACATGATTATCTCAATAGATGCAGAAAAGGCCTTTGACAAAATTCAACAGCCCTTAATGCTAA
AAACTCTCAATAAATTAGGTATTGATGGGACGTATCTCAAAATAGTAAGAGCTATCTATGACAAACCCAC
AGCCAATATCATACTGAATGGCAAAAACTGGAAGCATTCCCTTTGAAAACTGGCACAAGACAGGAATGCC
CTCTCTCACCACTCCTATTCAACATAGTGTTGGAAGTTCTGGCCAGGGCAATCAGGCAGGAGAAGGAAAT
AAAGGGTATTCAATTAGGAAAAGAGGAAGTCAAATTGTCCCTGTTTGCAGATGACATGATTGTATATCTA
GAAAACCCCATCATCTCAGCCCAAAATCTCCTTAAGCTGATAAGCAACTTCAGCAAAGTCTCAGCATACA
AAATCAATGTGCAAAAATCACAAGCATTCCGATACACCAATAACAGACAAACAGAGAGCCAAATCATGAG
TGAACTCCCATTCACAATTGCTTCAAAGAGAATAAAATACCTAGGAATCCAACTAACAAGGGATGTGAAG
GACCTCTTCAAGGAGAACTACAGACCACTGCTCAATGAAATAAAAGAGGATACAAACAAATGGAAGAACA
TTCCATGCTCATGGGTAGGAAGAATCAATATCGTGATAATGGCCATACTGTCCAAGGTAATTTACAGATT
CAATGCCAACCCCATCAAGCTACCAATGACTTTCTTCACAGAATTGGAAAAAACTACTTTAAAGGTCATA
TGGAACCAAAAAAGAGCCCGCATTGCCAAGTCAATCTAAGCCAAAAGAACAAAGCTGGAGGCATCATGCT
ACCTGACTTCAAACTATACTACAAGGCTACAGTAACCAAAACAGCATGGTACTGGTACCAAAACAGAGAT
GTAGACCAATGGAACAGAACAGAGCCCTCAGAAATAATGCCACATATCTACAACCATCTGATCTTTGACA
AACCTGACAAAAACAAGAAATGGGGGAAGGATTCCCTATTTAATAAACGGTGCTGGGAAAACGGGCTAGC
CATATGTAGAAAGCTGAAACTGGATCCCTTCCTTACACCTTATACAAAAATTAATTCAAGATGGATTAAA
GACTTAAATGTTAGACGTAAAACCATAAAAACCCTAGAAGAAAACCTAGGCAATACCATTCAGGACATAG
GCATGGGCAAGGACTTCATGTCTAAAACACCAAAAGCAATGGCAACAAAAGCCAAAATTGACAAATGGGA
TCTAATTGAAGAGCTTCTACAAAGCAAAAGAAACTACCATCAGAGTGAACAGGCAACCTACAGAATGGGA
GAAAATTTTTGCAATCTACCCATCTGACAAAGGGCTAATATCCAGAATCCACAAAGAACTCAAACAAATT

FIGURE 1 (continued)

TACAAGAAAAAAACAACCCCATCAACAAGTGGGCAAAGGATATGAACAGACACTTCTCAAAAGAAGACAT
TTATGCAGCCAAAAGACACATGAAAAAATGCTCATCATCACTGGCTATCAGAGCAATGCAAATCAAAACC
ACAATGAGATACCATCTCACACCAGTTAGAATGGCAATCATTAAAAAGTCAGGAAACAACAGGTGCTAGA
GAGGATCTGGAAAAATAGGAACACTTTTACACTGTTGGGGGGACTGTAAACTAGTTCAACCATTGTGGAA
GTCAGTGTGGCGATTCCTCAGGGATCTAGAACTAGAAATGCCATTTGACCCAGCCATCCCATTACTGGGT
ATATACCCAAAGGATTATAAAACATGCTGCTATAAAGACACATGCACATGTATGTTTATTGCGGCACTAT
TCACAATAACAAAGACTTGGAACCAACCCAAATGTCCAACAAAGATAGACTGGATTAAGAAAATGTGGCA
CATATACACCATGGAATACTATGCAGCCATAAAAAAATGATGAGTTCATGTCCTTTGTAAGGACATAGATG
AAGCTGGAAACCATCATTCTCAGCAAACTATCGCAAGGACAAAAAACCAAACACCGCATGTTCTCACTCA
TAGGTGGGAATTGAACAATGAGAACACACAGACACAGGAAGGGGAACATCACTCACCAGGGCCTGTTGTG
GGGTAGGAGGAGTGGGGAGGGATAGCATTAGGAGATATACTTAATGTTAAATGAAGAGCTAATGGGTGCA
GCACACCAACATGGCACATGTATATGTAACAAACCTGCACGTTGTGCACATGTACCCTAAAACTTAAAGT
ATAATTAAAAAAATAAAATAAAATAAAGAAAATATGTTTTATTAACAAACAGCATATTTTATAATGGCGG
TGATCAATATTTATTAAACACAAGGTTCTAGAGGGCTCTTCTGGTAGGATAATTCTAAGAAAGAGGTTCC
AGATGTCAACTTACATATTCCCTTATAAAACACAGCCCTGGCTTACACAGTATCTGGTGTACATGTCTCT
TCTCTCCAATGAACTATAAGATCTTTGAGGTAAGGGTTCAGTGCTGCACCACTCAGCTACACTAATGGCA
ATGTGCACACAGTGAGCACTCATTAAATACATCAGTTACAGTTCACTTGCAGTTGCTTGCTTACTACCAA
AAACCGGGGTCAATCATTATAAGCATTCCCATCCAACACCCAATTTGTTGCATGGGGAATGAACTTCAGT
TTGGGTCCCTTGCTATTAAAGCACTCAATACCCATTATTTGTTTGCATTTATGTCGAACTCATAGATGCA
GGATCTGAAAAGTTAAATGAAGCTTAACATAGGCATCCAAATAAAATTAATTAGAATTTATATCTCAACT
ATTTCTAACAGAGTTTGAGTAACAAGACTCAACAGAAGGAAAACAGGGTAATAACAGAGACTAAGAGGGA
AAAAAAGGAAGGCAGCAGGGAGTGAAGGCTGGAGAAGAGAAGAAGGAAGGAAAAGAAGGAGGGACAGAGG
GTGGAAACATCTATCTAAGCAAGAGCTTCTTCCTCAAGTCAAAAATTTCTGCAAAAAACAACATCTTTTT
GGACAAATTTACATGATGCTTCTAACATCTGCTCATTGTGAAAAATGCAGGATAAAAACCTACAAATTCA
GTATTTTTAGTATTTTTATCTAAATTTATATTTCATCAAAACAAGATAAATTTGAAAAATATTAATACAT
ATATAGGCAAGACATTTCCTTACTTTGCGGAAATATGCTCACATAAATAATCCATTCTTTGCCAAAATAG
AGCCCTTCCAACACCTGTTCCCCAATCTCCAAGGCAGGGTCTTGGTCCATGGGTTAGAATCACTAAAACA
CACAAAATACAAGGAAATGTATCTATTAAGCACCATTTGGATTCTAAGATGCAAGTAAGAAACCTAATTT
GAAAGGGCTTACATAATAAAGGTGGTTTGCTGGCACATGCAAATGGAAAGTTCAGCGGCTTCAGGTTGAG
TTTGAGTCAGTTGCTCTATGATGAAAACAAGGGCCTATTTTCTCTCTCTTTTTTTTTTTTTTTTTTTTTT
TTTTGGGAGACGGAGTCTTGCTCTGTCGCCCAGGCTGGAGTGCAGTGGCATGATCTCGGCTCACTGCAAG
CTCCGCCTCCTGGGTTCACGCCATTCTCCTGCCTCAGCCTCCCGAGTAGCTGGGGCTATAGGCGCCCACC
ACCATGCCCCGCTAATTTTTTTTTTTTGTATTTTTTAGTAGAAACGGGGTTTCACCATGTTAGCCAGGAT
GCTCTCGGTCTCCTGACCTCGTGATCCGCCCGCCTCGGCCTCCCAAAGTGCTGGGATTACAGGCGTGAGC
CACCGTGCCTGGCCAATAAGGGCCTATTTTCTTTCTTTCTACTTCGTCAACCACATCCTAGGGGTAGCTT
CCCTCGTGACAGCAAGGTAACTCCAGCAGCCCCAAGCTTCATGTCCCAAACATCCAGAAGGACACAGAGA
GAGGGCCGTCTTGGGGAGGTCTATCAGAAGACTGAAGAGCCTTCTTCCCAAAGTCCTCAGCAAGCATGCT
GGTGGCCTGCACAGGTCACATGCCCAGCCATGAACAAACCTCTTGGCATGACTGCCACTGGGTTAATCAC
TGTGCAACAGGTGTGGGGTTTACCTGACTGGGCTTAAACAATCAAGATCCATCCCTGGAGCTGGGGGTGG
GACCAATCCTTCTCCTACCAGAAGACAGAAACAAACATTCCCTGTTTCCTATGGAAGGGACTGGGGAGGG
AGGGAGAAGAGACATTGTGAGAAGGGGAACAATTAGAATGCCCTCCACCCTTCACCTGGCACTGAATTTG
ACCCTGTGATTCCCAGTATCAAGGGAAAATATGGAAATGTATTTTAAGTGACACTATTTTTATCGTTTAA
CAAAGACAAATGTTTATTCTTATACAGAGATAAATTCTTTTGAAGGGAAACCCAAGGAGAAGAATGTCTT
GGAACTGTGTTTAAGAGAAAATAGGTAAAGCAGGAGGCTTAGTTTGGAAAGATGCAGTCACACTCAATAG
GCCATTCCTTTTTTTTTTTTGAGACAGTCTCTTGCTCTGTTGCCCAGGCTGGAGGGCAGTGGCGCCATCT
TGGCTCACTGCAACCTCTGCCTCCCAGGTTTAAGCGATTCTCCTGCCTCAGCCTTCCAAGTAGCTGGGAC
TGCATGTGCATGCCACCATGCCAGGCTAATTTTTGTATTTTTTTAGTAGAGATGGGGGGTTTTGCCATGT
TGGCCAGGCTGGTCAACAGGCCATTCCTACATGGATCCTCCAGAAGGCAGAGCATGGGACAGTAAATCAT
ATCATAATCCAGTGAAGTTACTTTGGCAGAGGGCTGAGATGATATAGCTCAGATGCTTTCCCTTCAAATC
ATCGAACTTACTGCAAAGAGTAGTAACTCACATATCTTAGAACCCCTTTTTTAATGTTTATTTTTGTAGG
TACATGGTAGGTATATATATTTATGGGTTACATGAGATATTTTGGTACAGGCATGTGACGCATAATAATC

FIGURE 1 (continued)

ACATCAGGGTAAATGAGGAATTCATCGCCTCAAGTATTTATCCTTTGAATTATACTGTTATTTGTAAATG
TACGATTATTTTCTACAATAGTCACCCTGTTGTGCTGGCAAATACTAGGTCTTATTCAATTTTTTTGTAC
CCACGAACCATCCCTATTTCCCCCCCGTCACTCACCCTACTACCCTTCCCAGCCTCTGGTAACCATCCTT
CTACTCTGTATCTCGATAAGTTCAATTCTTTTAATTTTTAGCTCCAACAAATAACTGAGAACATGCAAAG
TTTGTCTTTCTGCTCCTGGCTTATTTCACTTAACATAATGACCTCCAGTTCTATCCATGTTGTTGCAAAT
GACAAGATCTCATTCTTTTGTATCGTTGAATAGTACTTCATTGTGTATATGTACTACAGTTTTCTTTATC
CATTCATCTGTTGATGGGCACATAGGTTGCCTTCCAAATCTTGGCTATTGTGAATAGTGCTACAATAAAC
ATAAGTATGCAGATATCTCTTCGATATACTAATTTCCTTTTTGGGGGTATATACCCAGCAGTGGGATGGC
TGGATTGTATGATAGCTCTATTTTTAGTTTTTAGAGGAACCTCCAAACTGTTCTCCACAGTGGGAAATTA
CATTCCCAGCAACAGTGTACAAGGTGTCCCTTTTCTCCATATCCTCACCAGCATTTGTTACTTATTGCCT
GCCTTTTGGATAAAGGTCATTTTAACTGGGGTGAGGTGATATGTCCTTGTAGTTTTGATTTGCATTTCTC
TGATAAATGATGCTGAGCACTTTTTCCTATGCCCGTTTGCCATTTGTATGTCTTCTGAGAAATGTCTATT
CAAATCCCTTGCCCATTTTTAATGGGATTATTAGATTTTTTTCCTATCGAGTTGTTTGAGCTCTTTATAT
ATTCTGATTATTAATCCTTTGTCAGAAAGGTAGTTTGCAAATATTTTCTCCCATATTGTGGGTTGTCCCT
TCACTTTGTTAATTGTTCCCCTTGCTGTGCAGAAGCTTTTTAACTTGATGTGATTCCATTTGTTCATTTT
TGCTTTGGTTGCCTGTGCTTGTCCAGGTATTACTCAAGAAATCTTTGCCCACTTCTGTTTCATGGGTCTA
TGTGTCTGTTTTTATGCCAATATCATGCTGTTTTGGTTACTATAACTCTGTGTATAATTTGAAGTTAGGT
AATGTGATTCTTCCAGTTTTGTTCTTTTTGCTCTGGATAGCTTTGGTTATTCTGGGTTGTTTGTGGTTCC
AATAAAAATTTTTGAATTGTTTTCTCTATTTCTGTGAAGAATGTCATTCATATTTTGATAGAGATTGCAT
TGACTCTGTAGATTGCTTTGGGTAGTATGAACATTTTAACAATATTTATTCTTCCAATCCATGAATTAGA
CCCCTTATGTATCATATTTATAAAAGTAAGCTCAAGCACTTTAAAATCATGACCTCTAGAGTGTTTTAAA
TTACTGTCATTATCAGATTATCCTCTGAGTGTGCATGTGTGTGTGTGTACATGTGTGCACCTGTCATTAT
TTCAAATTTTAAAATATTTGAGTGCTACTAGATGCTCAGCTCTAAGAGACAGGGTACAAGGAGGAAGAGT
TCAAAACTATAGTTGTCTCTGCCCTCAAGAAGTGTAACAACTACTACTACCATCAACTGGATAAAATTAT
AGGATGTCAGGCACTGTGCTTTACATTTATTTTCTCATTTAATTTGATCCTCACAATAACCCTATGAGCT
AAATATCAACTTGATTTTCCAAATTGGGAAACCAAGGCTTGAATGGCTAAGTCATTTGACTCAGTCACAC
AAGCAACAGGCAACAGCAAGGATTCAAAGCCAGGTACTCCCAATTCCAAAGCCTAGATTCTTAACCACAG
CACATCTGGCTGACAAGAAAACACAAACATCCATTAAGGGTGAGGAGTAGAAAGAGTATATTTACAGTGA
AGAGCTAAGTCCTGAGATATGGAGTAAAGTGGCTTAGGAGAAATCAAAGAATGCAAATAGGGTGAGGAGG
AGCCACATACACAGCTGTTAGCTTTGTGAACCCTGTGAACACTGATGCCTAACTGATCAAACACAATCTG
TCTGCTGGCCTCTGACCCATGATCTACTAGTGTACTATGTCTTTAGCCACTGACAGAATGGAAAACCAAT
GACGTTTTGACAGGCCTTAAGACCTTTCAAAGTTATCTCCAAGGATGGAATCAGCTCTTTCCCTGATGTG
GACAGACTTCTATTCTGTTCTAGACATAAGGCCATATATGGAGGAAGTTTGAAATCCTCTGGCCAAATAC
TAGATAGTACTTCCATTGTTTAATAATTAAGTGATTTTTATAACCCTATCCCTAAGAGCATATGGCAATT
GTCTTTGCCCACAGGATCAACTGTCACTAACCTTTTAGCTTGGTGGAAAAAGCTAAATGTCTTATAATGT
CTAAAAAAATGTAATACCACTTCCTCTGTGCTTGTCTCCATGTACCAGGAAGTCGTGGGTCTAAGTGGAT
GTGGTGTCCCTCTCATGCCTCAGCAGTCCCTTTACAAAGCAGCAGACTTCTGGGTACCCAGGTCGGGGCA
GACCTCCCAACCTTCAGGGTATGCTTCTAGGTTCCCAGTGCTCCAAGAGAGGGAGAAATACTTCCTCTAT
AAAATAATGGGGAGTCAGAGGCATATGGGATTTCCCTTTGCTTCCATGAAATTAGGAGAAAGCACCAACA
CTTTCTAGTAATTCCACAGTGAATAGGATGTGCTACCAGCCCAGCATCAGTAGGGCTTCTCTTCATTCTC
AAGAAGTGTAATTACCTGACGTGGCTGCCTGGAATTAAGATTGCCGCTATCAAGGTAATAAGAAACAGTT
CCATTCTTCCCCATGAGCCAATTATTATCAGGGTCACATCTGGAACCTTGGCTTCATTTTCCCGATTCAA
TCCATATTTGAATGACCACTATGGACCAGGTTCTATGCTAACATCTCACTGACTCAAACAGTCTTAGGAA
ATGGATATTATTTCTGTCTTACCTATGTGGAAGCTAAATAAAGCTCAGGAAAGTTATATCTTTTGTCACA
GAGCTGGACAATTATAGTTGGATACCAGACTGAATCTCCTGACACTATGTTCTGGGCTGACTCCACTATG
TGCCACTGACTCCCGTAGTGCTGAGGTTTGGGGCCTTATAATATTATTATTATAATAACAATACATGGGA
TTTCAATGGTCATCCTCATAATCAAGCTCTTACTCTACTCTCAAAGGAGAAAGAACATATCATGTTGAAG
GGGGCTATTAGAAGGCAAATGTGGTAAGTGCTGCAATGAATGGACACAAGCAGTTTAGAAACCCTATGAC
GAGGATCAACTCTGACTGGAGTGAGGATGAAGGAAAACTTAAGAGATGTGAAGCCATCCACTGGGGAGGA
GATGCTTTTGAGGTTAACAGAAGCTCTTAAACACAGAGTTGGAAGCAGGCAAACACTAAGGGATTCGTGG
ACCACCTCTTACATCAGGGTTTCTCAATCTTTTTATTGACATTTAGGGCTAGATAATCCTATGTGCTGGG

FIGURE 1 (continued)

GGGCTGTCCTGTAAATTGCAGGATATTTAGTAACATCCCTGACTAGATGCCCACTAGATCCCAGTAGAGC
ACACTGTCCCCAGGTCATGACAACCAAAAAGTCTCCAGACACTGCCAAATATCCCCTAGGGGACACAGTT
ATCCCTAGTTGAGAACCAGTGCCTTTGGTGAAGATGTGCCAGAAACTGGGGATTGGCTAAATGCGGAGGC
TGGGGAGGTGCAGAGCAAGAACAGGAAGCCATGAACCAGATAGGAAAGAGGGACAGATGTGTGACTCAAG
TCCTCTCAGCAACTCCCTCAGGTATGGACTCTGACTACCTTAAAGCAAACGGAGGGTCAGGCACAGTAGC
TCACGCCTGTAATCCTACCACTTTGGGAGGCTGAGCCAGCAGGATCACTTGAGCCCAGGAGTTCAAGTCT
AGCCTAGGCAATAGAGTAAGGCCCTGTATCTGTTTTTTAAAAAACACATATTTAAAAAAAGACAAATGGA
GGCAAATAAGATCCCATGATGAGGGCCCTTTGATGAATGTCCAGTAGGACCCTGATTGGGAGTAGGACAT
TTATAAGTGGAGAGGATGGATTCTAGACCCACGCAGCTTGGAACAGAAAAACCCTTACTCTCTTTCTCCT
TTCAGTAAATCAAAGAAAGAGAAGACAACCAGGGGGAATGCTAATAGAATAGTCATAATGAACCTGGAAT
TCCCACGCCCATTTGGGAGGATTGGAGAGGAACTGGATAAGGAGAAATACTGATGTGTGTTGTGTCTGTG
ACTGCAGTGCCATCCTTACCTTCTCGGCCATCTCCTATTCCCTCACCTCTCACCCTTGGAAGGGTTTTGG
CCCAGGAAAAGCAAAAGGAGTTGGGATACTTACTTCAGGGAGGGAGGAAGGAAAGAAAAGAAGGGAGTAG
AGATGAGAGAATTCTGAGGTTCAAAAGATATCTATTGACAGTGTTCACAAAAAGGACCATGTTTCCCAGT
AAAAAGAAAACAAGGTAAAGCTGAGGCTGGGGATGGGGGTTGAGGAAAGGGAAGGGGCCTACAAGTAAAT
GTTTACAAAATGCCCACTGAGTGTCAATTCTGGGCAAGGCACATTGCATGAGTCACCACCTTCAATTTTC
ACAGCATCATGTAATACCTATATATGAAGTGGTTATAACAAGCTCCTTTCTATAGAGAAGGAAAGTGAGG
TTCAGAGGCATCTTCACAGACTGAGGGGACTCCCAGCGTGGCCAGGGGCTTGTTTGGCAGACTCCTCCAT
GCTGTGCCTCCTCACACTTCAGCACCCACAGCCTCTTGCCTCATGCAAGCTGTAGCTGCCTGCTTGTCTG
TTTGCTCTGCAACATTAGAGCAGAGGGGCTCTAATCTGTGTCAGGTGCTGTGCTTTGAGTTCTGTGACTC
TAGTATTTCCTTATGTGCCAGGCACAGGCCCCAGTGATACAAAGAAGGGAGCAAGAGTTAACGCTGAGGT
GAACAAAGGACCCATGGAAGCCCAGCTGTGTGAATTTACAGCACAACTAATGAGCACACCCAGTTACATA
ACTGCCTCTCCTGCTCTGCTCCTATGCTCAGCAGCCACTAGAGGAAAGCAGGGCTGTCTTTCTTTTCCTG
TGCTATATATAATTCCAACTGTTTGGGCAGGGAAATGTGCTACAGCTCCACAGCTCAGTTACATTAGATC
TTAATTTTTTCTTAAAAACCTAGCAATTTCTAACAGTGATGCCACAAAGATAATAATACAGTAATCTTAA
GATTGAGATACTTTACCCACATTTCCTGCACTTTTCTACCTTGAAAACACTCATTATTTCTGGTTCCACT
TTGAGAAGCAGCAAGCAAGGAAAGGGTGAAAATGTGAGATGCTGAAGAGACAGCTTGCAACATTCCATAA
TTACAGCCTTCAATGCTGGAACCTCAAGTCTCCAATATCAAATGGAACAGTACTTCCCCTTGGTATCTAA
CTAGGAGCTGATCCATTAACCAGGAATATATTTTTGATATAGAGTAGGCCAGTTTTGTTTCTGGTTCTTT
TGCATCTCCTTTCCTAGGCCCTAAACACAGACTCCATGACCTCATGACAGTAGAATGAATGCTGCATAAA
GAGAATCATTCATTCGTCCTGGGACTTCACTGAAGATGATTTTTGCTTAGTAAGCCTCTTCTTCAGATAT
AATACTAAAAGGTATGTTTTCTGAGACCTATTAAAGCACACATTTACTAAAATTTACATTAAGTTCATGT
CAGTCCTAAAAGGTTCTCTAATTTCTGAAAGCCATAGTCTGTTATTCTAATGTGAATTGTTACACACACA
TACAGACACACCTTGAACATTTTAAAATTACATTTATTTAAGCATACTCACTCACTCATACTTTTTGCCA
ATTTGGTTGGGCTTTCCCCTAAACCAATTCTTCTAAAATGGTGAGACTTTAACAAATAAAATGATATAGC
TGATATTTTCATAGGGTAATAGGTTAAGAAGAAAAAAATCCAGGCTTTTGAAATACTAATTGTATTAGCA
TTAATACTAATACCTAGGCCAGGCGCAGTGGCTCACACCTGTAATCCCAGCACTTTGGGAGGCTGAGGCA
GGTGGAACACTTGAGGTCAGGAGTTTAAGACCAGCCTGGCCAACATGAGGAAACCCCATCTCTACTAAAA
ATACAAAAATTAGCCAGGCGTCGTGGCACATGCCTGTAATCCCAGCTACTCGGAAGGCCAAAGCAGGAGA
ATCACTCGAACCCAGGAGGTGGAGGTTGCAGTGAGCCGAGACTGTGCCACTGCACTACAGCCTGAGGGAC
AGAGCAAGACTCCATCTGAAAAAAAAAAACCAAACAAACAAACAAACAAACAAAAAAAACTAATATCTAA
ATATTAGCAGTACTATGATTTATAGACATGAACTCTTATAAAGAGTATGTATATGGCTGGGCATGGTGGC
TCATGCCTGTAATCCTGGCACTATGGGAGGCTAAGGCTGGCAGATCGCTTGAGCCTAGGAGTTTGAGACC
AGCCTGGACAACATGGCAAAACCTTGTCTCTACAAAAATACAAAAATTAGATGGGCATTGTGGCGTGCGC
CTCATGCCTGCAGTTCCAGCTACTTGGCGGGGCTGAGACAGGAGGATTGCCTGAACCCAGGAGGTCGAGG
CTGCAGTGAGCCAAGATCATGCCACCGCACTCCAGCCTGGGTGACAGAGGGAGAACCTGTTTCAAAAAAG
AAAGACTTGCTTAATACTGGGCAGCTCAGTTATAGCAAGTACTAGTCAAGGGTGGCATGTCACTGTGTTC
AGAGTTGGATGAACCTGGGTTCTAATCTGGACTCAGCTACTTCCTAGTGTAGGTCATTTGGGTCTTGGGC
AAAGTATTGAACCTCCCAAACCTCAGTTCTCTTTTGCACAATGGAAATCATCTGAATATAGACAAGATAG
GGCCCACTATAAAAATTAAACAAGATAGTCTGTGTGGAAGTATCTTTAACAGGCATTAAGTGCCTGTTAA
GTGTCTTTAACAGGAGAATTAAGTAGCATGTTCAGGCTTTTTGCCTCCTTCCTCTTCCCCTCCACTCCCC

FIGURE 1 (continued)

AGTGACCAACTTGCACCCTGAGTAAGGTTTTGCAGCACCATCCTTCTCCTGTGGCTTGTAAACCTCTGCA
GTAACTTCAGCAATCTACACTGCCTGCACCCTGCCCTCCCTGTATGCTCCCCTGAATCACAACCATATTT
GCCTTTCTAGAGCACATATCATTGTCTTCAGTGATTCCCTGCAGGACAAAGTCTGCCCACTTCAGCCTGG
TATCATGATCCTGTCTTAGTCTGGTCCAACCCACCCTTTCTGAACAGTTCCTTACAAACCCACATCTTCC
TACCTCAACTCTGCCTAGGCCATTCCCCTGCTTCAAGCTCTTACAGAGCCTCCCATGGCCTACAGTATAA
ATTCCTAACTGTTTCAGGTGGCATTTGAGACCGATGGTATCAGGTCCCTGCGCCTCTCCAGTTTCACTGT
CTGCTACTCGTTTCCCTCCTTATACTTTACACCCAAGCGTAAATCTACTTATAGTACCTGAAACCCCATG
CTGGGTCATCACTCTTCAGCTTTACATATACTCCTCTCTTTGACGAGAATACTCTTCTCATCCATTTGGC
AAATTCTTCAACAGACTTCAAACCTCTCTCAAATGCCTCTACTTCTGTGGTACAGTCTGTCCAGAACTGT
GTCTTGTACATTTTTCTACTACTTTGCACCTGTGCCTGTCATACAACGATTTCTCCAGTTTCTCCGGTTT
TTTTTTTGTAATTCACTGACCATTATTAATGTCTTCTCTGCTAAAAGTATAACAACACTCAGCTTTGCAC
AGAGCAGTTACTTGGGAAATGTTTGCATTGCTGAACACAGGCAGCTTCCAATCTCATGGGAACATCAAAT
GAAATGCAGAGGATACATGCTATACAACACAGTCAAGAGGACTGAAAGCAGGCAGCAGGAGAATTCCACA
ATATTCCTGTTTAAAATGTTAAAATGTTGGTGGCTGCCAGAGCTCAGGAAAAGAAAATTTTTTTATGTGG
TTACAGCTCACTCTAACGAGTCAATTACATTGACCTAAAGCCCATGGTGCTCAAAACTGTATTTCTCTCT
CCAAAACCTCATTCTTTTATAAAGCTCCCTCCTCTGTGGAATGAATGTGGGCAATCGCTTTTGCAGTGTT
TGACGATGCCAGTTTATGGCTATGTTTTTCTGTTCACTGAACTGGCTCATTTCTTCAGGAGAACAAACTG
TTCTCCACTGAAGCAGGAATTGGCTGGGTTCTAACAAAAAGATTTTTCCCCCCTGACAGTGTTTTTGCAA
AAGACCCAAGTCAATTTATAGCCAAGTAACAAAAGGTCAGAAAGGTTAGTCAAGCAATGGGCGTAATTCC
TGTGTGTCACAGCCAATAAAGGAAATGGGTGGGGATAAATAGTATGCAATTTTAACCTGAAATTATTTGT
GCAAAACTATTCTTGTAAACTATACAAAATTACCCATGACTTCCACTATATAGGATTTCTCACTCTGATT
TTTTTAAAGGTACATTTACTTTGGAAGAACTGAGATGACCTCAAATTCCTCATTCACAAATGGAAAATGT
TAAAAACTTTCTTCACACTAATATAAGAAAAACTTGGTCATTGTTTTGCAGCCCTGAAACAGAATTGTTC
ACATAAAAAAAAAAAATCTCATAGTTAAGTCACAATTAAATACAATTTGCATGACTGAATTTAAAATAAAT
TGCAAAATTCCCTTGCCAAAAGGGAAACAACATTGACCAAAAGGATAGGTCAAGAAAAGACCCTACAAAA
GTGACAGTTCCTCTGTTTTAATCATGCTAAAAGTATAACAAACTACTGCATTATTCAGTGAGCATAAGAA
CAAGAAAAGCCTGCCTTTAAAGCAGACACGAAGAACTGACATCACCAGCCAAGCAAGCGGAAGGCAGATG
AGTAATAGCCTGCACTGGGCGGCCAACCAGGCCCAGGCCCATCAGTCTGTGGAGTAAGAAAGCCTTTCAG
ATATCAAGGTCGTTGGGAGGCCTCCTTCCCCCAGTTCTCCAATACAAAGTCTAATCTACTCACCATTTAA
AACAATCTTAGCATCCAAAAGATGAATGGTTAAATAGAACCCTGTCACCGTTCAGACAAGATGGTCTAAA
CCCATTTCTCTCCCCACCTCCTTGTAAGCACAACTGTAAATCCTGAAAATAACACAAAAGGCAACCAAAG
GAGAAGTCTGAAAGAAAAAGGAAGGTGAATTACTTAGGGACCCAGGATTGGAGGAACAACATAGCAGCAC
ATCTTATGACCACACCCCCATTCAATAGAAGAAGGTGGCCGAGGGTGTTTCCCAACCCCCAACCTAGCAA
CAGAGGGCAGCAGAGGATTGAATGGGAGTTCTGCCGACAATACCAAGCCAGCTGGAAGCACCAACAAGGG
GGATAGCTCAGGACCCCACTAACAATAAAGCAGTCTGGGGAAACACTTTTCCCCCCAACTACAGGGCCCC
CAGGAAGCAAGCTGCATCCCAGCAGGATGGAGACTCCCTCCTCTACCTAGATATCAGGCAGCATGGCCTG
GGGAAACTCCTTACCCCCATCAGACAGCACCAACAGGGACTAGTGGGAGCCGTGGCAGCACCAGATAAAC
CAAGTGGACCAAAAGAGTACTGCAAAGGCTCTGAAAAGTAAATCATCGTTGGAACCACAAGAGTAAATCC
CAGCTCACATGCTGCATCTAAACACTGTGACCGCCTGCTAAAATGGAAGATTTAAATAGGACCCAGACTC
TCTTAATAGACAAAATGTCCGAAGTAGATTTTAAAAAATCACCTGTTGGCCAGGCGTGGTAGCTCATGTC
TGTAATCCCAGTACTTTGGGAGGCTGAGATGGTTTAATCATTTGAGGCCAGGAGTTCGAGACCAACCTGG
GCAACATGGCAAAACCATGAAGATGGACTGAAAACAGACAGAACCTCCAACACTTATGAAACAATAGCAA
AAGATCCAATATTCATATTATCAGAGTCACAGGAGAGAATAAAAAGAAGGGCTGAAAGAGTATTCAAAAA
GATAATGACTGAAAATTCCCCAAATTTGCTGAAGGACATAAACCTAGATTCAGAAGGTGAACATATCCCA
AATAGGATAAACTCAAAGAAATCCACACTAAGACACATCTTAATTATATTTCTGTAAATTAAAGACAAAG
AATAACTCTTGAAAGCAGAGAAAAACAACATACTACCTATAAGGGAATATCAAGCGACAACAGGTTTCTT
ATCTAAAACCATGGAGGCCTGGCCGGGCACACTGGCTCACGCCTGTAATCCTATGACTTTGGGAGGCCAA
GGCAGGCAGATCATTTGAGGTTAGGAGTTTGAGACCAGCTTGGCCAACATGGTGAAACCCCGTCTCTACT
AAAAATAAAAAATAATAACAAATAAAATTAAAAAATAAAACCATGGAGGCCAGAAGGAAGTGGCACAACA
TTTTTATGGTTAAAGGAAGTTTTTCAAACAGAAAGGAAATGATTAAAAGAATTCTGAAGCATCAAAAGGG
AACAGAAAACAACAGAAAAGGCAGAAATATGGGGAGATATATATATATATAGATTATCCTCCTGTAGTCC

FIGURE 1 (continued)

CAGCTATTTGGGAGGCTAAAGCAGGAATATTGCTTGAGTCTAGAAGTTCACTTCTACCCTGGGCAACATA
GCAAGACTCTGTGTCTTAAAAAAATTAAAAATTAAAAGGGGGAAGGTAAAGGGACCTGAATGGAAATCAG
GTTTCCACATTTCACTCAAAGTGGTAAAATACTGATC

FIGURE 2

MAGAASPCANGCGPGAPSDAEVLHLCRSLEVGTVMTLFYSKKSQ
RPERKTFQVKLETRQITWSRGADKIEGAIDIREIKEIRPGKTSR
DFDRYQEDPAFRPDQSHCFVILYGMEFRLKTLSLQATSEDEVNM
WIKGLTWLMEDTLQAPTPLQIERWLRKQFYSVDRNREDRISAKD
LKNMLSQVNYRVPNMRFLRERLTDLEQRSGDITYGQFAQLYRSL
MYSAQKTMDLPFLEASTLRAGERPELCRVSLPEFQQFLLDYQGE
LWAVDRLQVQEFMLSFLRDPLREIEEPYFFLDEFVTFLFSKENS
VWNSQLDAVCPDTMNNPLSHYWISSSHNTYLTGDQFSSESSLEA
YARCLRMGCRCIELDCWDGPDGMPVIYHGHTLTTKIKFSDVLHT
IKEHAFVASEYPVILSIEDHCSIAQQRNMAQYFKKVLGDTLLTK
PVEISADGLPSPNQLKRKILIKHKKLAEGSAYEEVPTSMMYSEN
DISNSIKNGILYLEDPVNHEWYPHYFVLTSSKIYYSEETSSDQG
NEDEEEPKEVSSSTELHSNEKWFHGKLGAGRDGRHIAERLLTEY
CIETGAPDGSFLVRESETFVGDYTLSFWRNGKVQHCRIHSRQDA
GTPKFFLTDNLVFDSLYDLITHYQQVPLRCNEFEMRLSEPVPQT
NAHESKEWYHASLTRAQAEHMLMRVPRDGAFLVRKRNEPNSYAI
SFRAEGKIKHCRVQQEGQTVMLGNSEFDSLVDLISYYEKHPLYR
KMKLRYPINEEALEKIGTAEPDYGALYEGRNPGFYVEANPMPTF
KCAVKALFDYKAQREDELTFIKSAIIQNVEKQEGGWWRGDYGGK
KQLWFPSNYVEEMVNPVALEPEREHLDENSPLGDLLRGVLDVPA
CQIAIRPEGKNNRLFVFSISMASVAHWSLDVAADSQEELQDWVK
KIREVAQTADARLTEGKIMERRKKIALELSELVVYCRPVPFDEE
KIGTERACYRDMSSFPETKAEKYVNKAKGKKFLQYNRLQLSRIY
PKGQRLDSSNYDPLPMWICGSQLVALNFQTPDKPMQMNQALFMT
GRHCGYVLQPSTMRDEAFDPFDKSSLRGLEPCAISIEVLGARHL
PKNGRGIVCPFVEIEVAGAEYDSTKQKTEFVVDNGLNPVWPAKP
FHFQISNPEFAFLRFVVYEEDMFSDQNFLAQATFPVKGLKTGYR
AVPLKNNYSEDLELASLLIKIDIFPAKENGDLSPFSGTSLRERG
SDASGQLFHGRAREGSFESRYQQPFEDFRISQEHLADHFDSRER
RAPRRTRVNGDNRL

FIGURE 3 (continued)

GAATTCTAAAAACAGCAATAGAAAAGTGTCTAGTCACTTATAAGAGAACTCTCATCAGACTAAGAGTGGA
TTTCTCAGCAGAAACCTTACAGGCCAGAGAGAATGGGATAATACATTTAAAGTCCTGAAAGAAAAAACCT
GCTAGCCAAGGATATTATACCAACAACGTTATTCTTCATACATGAAGGAGAACTGACGTCTTTCCCAAAC
AAACAAGCTGAGGGAATTCATCGCCACTAAATTGGCACTACAGAAACTCTTTAGTCCTATGCCTGGAAGC
GAAAGAATAATATCTACCATCATTTAAAATATATATATATATATAAACCACTGGTCAAGCAAACACACAA
GAGATAAAACACAAATATTACCAAGACAAAAAAACCACCAAACAACAATGACAAACAATGAGAGAAAGAA
ACAAAAGATAAGTATAGAACCAGAAATCAATTAATAAAATGAGAGGAATATGCCCTCACTTATCAATAAT
AACCTTGAATGTAAATAAATTAAACCTGCCACTTAAAAGATACAGTCTGGCTGAATGAATTTTAAAAATG
ACCCAACTATATGCTACCTACAAGAATCTCATCTCACCTGTAAAGACACATATAGACAGAAAGTAAGGGA
ATGTAAAATAATATTCCATGCAAACAGAAACCAAAAGTGAGCAGGAGTAGCTATACCTATATCAGATAAA
ACAGACTTAGACCAAATGGACCTAACAGACATTTAAAGAACATTTCATACAACCACTACAGAATACACAT
TCTTCTCATCAGCACACAGAACATTGTCCAGAAGAGATCATATGTTAGGACACAAAACAAGTCTCAACAA
ATATTTAAAATTATAAATCATATCAATTATCTTTTCAGACCACAATCAATAAAACTGGAAGTCACTAACA
AAAGAAACTTTGGAAAGTGTACAAATACATGGAAATTAAATAACATGTCCTGGGAGAAATTCAGGATGAA
ATTTAAAAATTAAATAACCTGCTCAAGGAAGAAATTAAGAAGGAAATCAAAAAATTTATTGAAACAAATG
AAAATAAAAACACAACATACCAAAACCTATGCGATACAGCAAAAAACAGTGCTAAGAGGAAGGTTAAAGC
AATAAACACCTACATCCAAAAAGTAGAAATATTTCTTAAAAAATCTAACCATGCACCTAAAGAAACTAGA
AAAGCAAGAACAAACCAAAACCAAAATTAGTAGACGGAATAAAATAAAGATCAGAGCAGAATTAAACAAA
ATAGAGACAAATAAAATAATACGAAGGGTGAACAAAAAAGTTTGTGTTTTGAAAAGATAACATCAATAAG
CCACTTGCTGGAGTAATCAAGAACTCTTACACACTATTAGTGAAAATGTAAATTAGTATAGCCACTATGG
AAAACAATGTGGAATTTCTCAAAAATCTAAAAATAAAACTACCATACACTCCAGCCATTTCACTGCTGGG
TATTTATCCTAAAGAAAAGAAATCAGTATAACAAAGAGATACAAGCACTCCAATGTTTACTGCAGCACTA
TTCACAATAACATATATATGAAACCAAACTAAATGTTCAGCAATGGATGGATGAAGAAAATGTGTATAAT
GTATATATATATATATACACAATATGTGTGTGTATATATATATGTATATATGTATATGTGTGTGTGTATA
TATATACACACACACACAATGGAATACTATTCAGACATAAGAAGAATAAAATCATGTCATCTGCAGCAAC
ATGGATGGAACTGGAAGTCATTATGTTAAGTATTAAGTTTAAAAAGCCAGGCATAGAAAGACAAACACTC
ATGTTCTCACTCACATGTGGGAGCTAAAAAAGTTGATTTCACGGAGGTAGAGAGTAGAATGATAGATACC
AGAGGCCGGGAAGAGTAGGTGAGTGGGAAGGGGGATGAAGAGAGGTTGGTTAATGGGTGCAAAACATACA
GTTAGATAGAAGATATAACTTCTAATGTTTGATAGTGAACTAGAATGACTAGAAATGACAATGACATATG
GCATGTAACAAAGTAGCTACAAGAGAGGACTTGAAATGTTCCCAAGTGATAGAAATGATAAATATTCAAG
ATGATGGATATCCCAAATACCCTGACTTGATCATTACACATTTTATGCATGAAACAAAATATCACATTAC
TCCATAAATATGTAAAATATTATGGATCAATAAAAAATAATGTATTTGAAAAACTAACTTCTTTAAAAAA
TAAAACTGAACCCCTACATTACACATAAAAAATTGATGAAAACTAAATGTGTAAGAGGAAAAAAGCTTTA
TATTAAAGTTAATAGAAATACAGGATTTATATGCATATATATATTTATAAACCATGACTTGGTAAAATTT
CAAAAGCAAAAATAATAAGGCATATGCATGATAAATTTGGTTGTATCAAAATTAAAGATTTCTATTCAAA
GACATATACTATGGATGGTTCTCATAGATGAAAAAAATGAGAGAAGATTCTTATATGTCTTGGCAAAAAA
GTGAATAATATTGAGAAAATACAATGTCTAAATGTCTAGACATCGTTAATTGATAGGAAAATGACAGTAA
CTGCAATAGAACAATGGTCAAAAGGTCTGAATAAGAAACTGCAAACTTAGGAAGTATGGTCAGCTCTCTG
TACCTATGGGTTCTACATCAGTGATTCAACCAACTGAGGATGGAAAATATTCACATATAAAAATGAATGG
TTGTGTCTGTACTAAACATGCACAGACTTTTTTTCTTGTCATTATTCCCTAAACAATACAGTATAATCAA
TATTTACATAGAGTTTACATTGTATTAGGTATTATATGTAATCTAGGGATAATTTAAATCACATGGGAGC
ATATGCATATGTTATATGCAAATACTACACCATTTTATAACAGGGACTTGAGCATCTGCATATTTTGGTA
TTTGCGGAAGGTTCTGGATCCAATCTCCCATGGACACCAAAAGACTAACTGTATATGAATACATAAAGAG
ACACTCAAACTTACTAGAAATCAGAGACATGCAAATCAAAGCAAAGCAACATCACTTGACACCTATTGGA
TTAACAAAAATTGGAAAGATGGATAACCGATGGGGTGTGGAGACATAGGGGCCCTCAAGCGCTGCTAGTG
GGATTGTAAACTGCAGCAGACCCTGTGGAGAGCATCTGGTACATTTGACTAAACTTGGTATAATCCCACC
TGCAGTGTGATTCAGCAATTCCACTACTAGTTAGATATGCCAATAAATTTCTCATGCAGACTTCTAAGAC
GACATGTGTAATATTTATTACAGCATTATTTGGGGAAGTCTGGTGTTGGAGGTGAGATTTGGCAAGTTCA
TTGCAAGGAGAATGGATAGATAAAGGTTGATGGATGCCCTTCATAGGGTACTACAGAGTAAAAGGAAGCA
ATGGACTAGATGTACATGTAGCAACATGGATGAATCTTATAAACAGAATGGATGAATCTTATAAAATAAT
GCCAAGTAACAATATTTTTAAAAACATAATATCTTATATGTAAACTAATAGCATTTACATAAGTTGAAAA
TGTACAGACATAAAAAATAATATGCATTTTCCAAAAGCACTTATAAACAAAAAGACATGAGAATAGATGC
TTATGTTGAGAAGGAAGAATACAAAATGGGTACTGGTGATTAAATGGAATGAATTAAGAGTATTGATTGA

FIGURE 3 (continued)

ATGAATGAAGAGCGGGGATTTTACTGGATGAATGATGATTCAGGTATCATTACTGTACCTTCTGCATTTG
AGCATAGAAAATAGGAACAGAAAATTTGAATGGAAAGCAAGGAATTATATGAGCTCTTCCTCCAAAATTT
ACATCATATAAGTTGAAAACTGGGTGAAGTATAAGCAGGGAGCATTTTTGCAATGTTTAAAGTCCTAATT
CATAATTTTGAATTGTGTTTTTCTTAAATGGCTCCTTAAATATAAGACTATATTTTAGTGAAGCCAATAA
TGTTTTCATATTCCTATTGATGTGATCTACAAAGGCAAAAAACAATTTTAAAGACTAATTTCTAATCTTA
CTTTAATTCCTAAACTAGATTTTCAATGGATACTGTCTTTCCATGACATTAATTGCTACAAAAGAATACA
GAAATTTCCCCACAAATAAATAAATCAAAAATTATTTTTGACTTTAGCTATTTTTACAGACTTTTGTCCA
GTTTGTTGTATTTTATATAAATTCATTTCTTACACAAATTTGTACATAAAAGAAAAAATAAGAAATTCTC
CATATTTGACACTGATCCCTTCTGGTTGATTTTTTAATTTCTTGATGCAACTAGCAATGGTGCAGTGCAA
CCATAGCTCACTGCAGCCTCAAATTCCCGGGCTCAAGCCATCCTCCTACTTCAGCATCTTAAATATCTGG
GACTACAGGTGTGTACCACCATACCTGATGTATATATATGTATACATATATATATATAAAATATGTATAG
TATATATATTATATATATTGCATTATATATATAGCATTATATATATATATTATATATAGCATTATATATA
ATTCTATATTATATATAGCATTATATATAATGCTATATTGTATATAGCATTATATATAATGTATTCTATA
TTGTATATAGCATTATATATAATGTATTCTATATTGTATATAGCATTATATATAATGTATTCTATATTGT
ATATAGCATTATATATAATGTATTCTATATTGTATATAGCATTATATATAATGTATTCTATATTGTATAT
AGCATTATATATAATGTATTCTATATTGTATATAGCATTATATATAATGTATTCTATATTGTATATAGCA
TTATATATAATGTATTCTATATTGTATATAGCATTATATATAATGTATTCTATATTGTATATAGCATTAT
ATATAATGTATTCTATATTGTATATAGCATTATATATAATGTATTCTATATTGTATATAGCATTATATAT
AATGTATTCTATATTGTATATAGCATTATATATAATGTATTCTATATTATATATATAGCATTATATATAA
TGTATTCTATATTATATATAGCATTATATATAATGTATTCTGTATTATATATAGCATTATATATAATGTA
TTCTGTATTATATATATAGGATTATATATAATGTATTATATATTATATATAACATTATATAAAATGTATT
ATATATTTTATATATATAGCATTATATATAATGTATTACATATTATATATAGCATTATATAAAATGTATT
ACATATTATATATATATAGCATTATATATAATGTATTACATATTATATATAGCATTATATATAATGTATT
ACATATTATATATATAGCATTATATATAATGTATTACATATTATATATATAGCATTATATATAATGTATT
ACATATTATATATATAGCATTATATATAATGTATTACATATTATATATATAGCATTATATATAATGTATT
ACATATTATATATATAGCATTATATATAATGTATTACATATTATATATATAGCATTATATATAATGTATT
ACATATTATATATATAGCATTATATATAATGTATTACATATTATATATATAGCATTATATATAATGTATT
ACATATTATATATATAGCATTATATATAATGTATTACATATTATATATATAGCATTATATATAATGTATT
ACATATTATATATATAGCATTATATATAATGTATTACATATTATATATATAGCATTATATATAATGTATT
ATATATTATATATATAGCATTATATATAATGTATTATATTATATATAGTATTATATAATGTATTATATAT
TATATATAGTATTATATACAATATATTATATATAGTATTATATATAATGTATTATATATAGTATTATATA
TAATGTATTTTATATATAATATTATATGTATTTGTGTATATATATATTTGTACAGACAAGATTTGGCTAT
GTTTTCTGGGCTCATCTCAAATTCCTGGCATCAAGAAAACCCCCCACCTCAATTTCCCAAATTGCTGAGA
TTAGAGGTACCAGCCACAATACTTGGCTTTGAGCACATTTCTTTATTTGAGGTAAATCTTTCCCTTGAAA
ATATTTGATTTCCAACAAGTCAATTTCCTGATGATTTTTTTCCAGGAATTTATTTTTCACTGTTTCATTC
ACATTTAATGCTGTTTTTAAAAATTCTAGTTATTTTCAGCCATTCTTATGAAAGATGAATTGCCACAGGG
GTTCACCAAAAAGAAATGGAATGACATTTATCAAAGATAATCACAGTCATTAAAATTGGAGATACTGATT
TTACAGAGGATGATGACTTTAGTCCTTAAACATGACTATTTTTAATACTGACATATAGGCATTAGACTAT
AGGAAAAAAACATTTGTCAAAGAGTTTTGAAACTGCAATAATTCTGCTTTCTTCAATGAATATCTTGGCA
GAATCCTCTGGGAACAAAATGTCTAAGAGTACAGATTCTATGACAAGGACAAATTCTCACACATACTCTG
ATTATTCTAACAAAATAATCAGAGAGAGAAGAAAAAGAAACAAATGTCTATTTCTTCCAAGCTTCAGTTC
AGATCTATATTCCATGATTCTGACTACCATTGCGGGGTAGGGGCCAGAGTGAGGGTGTTTAATCAAGTTT
GATAATGAAGCAGTTGTCACTACATAAAGTGTAAAATAATATATAAAATATTAGAATTCAGATTCTAAAG
GTAAATCAAATATGCATTGCCTGATTATATAATGAGACCTTTTCCCTCCCTCTTTCTCTCCCTACCTGCC
CCTTTTCCCGTCTTCCTTTTCTTCATAACACTTGCAGAATGATATCGTAGGAAAAGACCAAAATATTATC
CTTAGATGAACCTGAACATATTGTGTGACTGTGAGGAAGTCACCAACCTTCATGGATTTAAATAACACAG
CTTTGGTATATAGTGACATGACAAAATTAGACTAAAATTTCTTCTAAATAGGCAATGGGTACTTTTGTCA
CCCTTTGGAATCTGAAATACAAAATAAAAAGCAGGAAGACTTAGCCAGAGCAGTCAGGCAAGAGAAAGAA
ATAAAAGGCATTCAAATAAGAAAAAAAAAAAAGGAAGTCAAATTATCTCTATTCAAGGATGATATTATTC
TATCCCCAGAAAACCCCAAAGACACTGCCAAAAGTCTCCTGTAACTAAACTTTAGTAAAGTTTCAGGATA
CAAAATCAATGAACAAAAATCAGTAGTATTTCTATACACCAATAACATTCAAGCTGAGAATAAAATCAAG
AATGCAATACCATTAAAAGAGCTGCAAAAAAAAAAAAAAAAGAAATACCTAGAAATACATCTAACCAAGG
AGGTGAAACATCTCTACAGGAACCACAAAACACTGCTGAAAGAAATCACAGATGATACAAATAAAAAAAA

FIGURE 3 (continued)

ATTTCATGCTCATGGTTTAGAAGAATCAATATTGTAAAAATGGCCAATACTGCCGAAAGCAATCTGAAGA
TTCAATGTTATTCCAGTCACACTACCCATGTCACTTTTCACAGAACTGGAAGAAGCTATTGTAAAATTCA
TATGAAACCAAAAAAGAACCCCAAAATGCAAAGCAATGCTAAACAAAAAGAACAAGCTGAAGGCATCATT
TTACCCATCTTCAAACTGTACTATAAGGCTACAGTAACCAAAACAGCATGGTACTGGTACGAAAAACAGG
CACATAGGACAATGGAACAGAACAGAGAACCCAGAAATAAAGGTGCACACCTACAGCCATCTGATCTTTG
ACAAAGTCAACAACAACAAGCAATGGAGAAAGGACTCCCTAATCAATAAATGGTGCTGGGACAGCTAGCT
GGCCTATGCAGAAGAATGAAATGACTCCTACCTTACACCATACACAAAAATTAACTCAAGATGGATTAAA
TATTTAAACATGAAATCTCAAACTATCGCACCACTGCACTCCAGACTGGGCGACAGAGCGATACTCCGTC
TCAAAAAAAAAAAAAAAAAAAAAAAATTCCCAGAAGAAAACGTAGTAAACACCCTTCTGGACGTTGGCTT
TGGGAATTAATTTATGACTAAGTCCTCAAAAGCAACTGAAACAAAAACAAATATTAACAAGTGAAACCTA
ATTAACTAAAGAGCTTCTTCACCACAAAAGAAACTATCAACAGAGAAAAGAGACAACGTACAGAGTGGCA
GAAAATATTCACAAAGTATTCATCCAGCAAAGGCCTAATATCCAGAATTTATCAGGAACTTAAACAATTC
AACAAGGAAAACCAATGCCATTAAAAAGTCAGCAAAAAACCTGAACAGATGCTTCTCAACAGAAGACACA
CAAGGGGCCAAAAAACTATGAAAAAATGTTCAACATCACTAGTCATCAGAGAAAAGCAAATCAAAACTAT
AATGAGATTACATCTCACAGCAGTCAGAATGGCTATTACTAAAAAGTCAAAAAACAATAGATGCTGGTGA
GACTGCAGAGAAAAGGGGAAAAGGAAGGCTTATACACCGTTGAAGAGAATGTAAATTAGTCTAGCCATTG
TGGAAAGCAGTTTAGAGATTTCTCACAGGAGTTAGAACTATTATTCAAACCAGAAATCCCATTACTGGGT
ATATATTTAAAAGAAAATAAATTTTCTACCATAAAGACAAACATGCACTTGTATGTTCATTGCAGCACTA
TTCACAATAGCAAAGACATGGAATCAACCTAGGTGCCCGTCAGTGGTGGATTGGATAAAGAAAATGTTGT
GTGTATATATCATGGAATACTATGCACCCATAAAAAAGAATGAGATCATATCCTTTGCGGTAACATGGAT
GCAGCTGGAGGCCATTATCCTAAGCAAATTAACAGAGGAACAGGAAACTAAATACCACATGTTCTTACTT
ATAAGTGGGAGCTAAACATTGGGTACTCATAGACATAAAGATGGCAACAATAGACACTGGAACTACTAGA
TGGGGAAGAGAGGGCTGAAAAACAATCTATTGAGTACTATGCTCAGTACCTGGGTGATAAAATCAATTGT
ACTCCAAGTCTCAGCATCACACAATATACTCATGTAATGACCCTGCACATGTACACCTAAAATCTAAAAT
AAAAGTTGAAATTATTTTTTAAAATTAAAATTAAAATAATAAAATAAAATTAGAATAATTATTTTCACTT
CTAGTTCCTCCATTAACTTTTTGTATTTAAGAACTGGTTGTTTATGGTTGGGCATGGTGGCTCACAGCTG
TGATCCCAGCACTTTGGGAGGCCAAGGTGGGTGGATCACCTAAGGTCAAGAATTCAAGACCAGCCTGGCC
AACATGGTGAAACGCTGTCTCTACTAAAAATACAAAAATTACCCAGGCATAGTGGCACATGCCTGTGATT
CCAGCTACTCAGGAGGCTGAGGCAGAAGAATCACTTGAACCTGGGAGGCGGAGTTTGCAGTGAGCTGAGA
TTGCATCACCGTACTCTATCCTGGGCAAGAGAGCGAGACTCCATCTCAAACAAACAAACAAACAAACAAA
AAAGAACTGGTTGTTTCTTATCTTTAGTGTGATCGGAAAGTTAAGAGGGAAATTCTGGATCACCATTCCC
GAAACAAAAGAATAACTCTAGAAATAAAGTTCTAGTCATTCGGCTGATGTCAGTTGGTGAAATTGTACAG
CAAGAAGATTTTACTGGCATTCTTTAACACTGATTGCATACTCTATACTCTAAGAAATTAAAACTAGGGA
ACCTGAGGTCATTTATCTGGACAAAGGGAAAAAAAAAGTCCAAGTTATTCGACTTAGAACAGGATGAATC
CTGACATTAAAAACTTCATTAACAACTCACACTATCACACGCTTTTGTGTACTGAGACATGTAACACTAA
GGCAAATCAATTGGAACGGGGATATGTAAACAGGGGTATGGCCACTTGGGTCTCTGAGGACAAAACAGCA
TCATGTTATAAGAGTGCTCATGGCTCACGCCTGTAGTCCCAGCACTTGGAGAGGCCGAGGCGGGCGGATC
ACGAGGTCAGGAGATCGAGACCATCCTGGCTAGCATGGGGAAACCCCGTCTCTATTAAAAATACAAAAAA
AAAAAAAATAGCCGGGTATGGTAGCAGGGGCCTGTAGTCCCAGCTACTCAGGAGGCTGAGGCAGGAGAAT
GGCGTGAACCTGGGAGGCAGAGCTTGCAGTGAGCCGAGATCGCGCCACTGCACTCCAGCCTGGGGCGACA
GAGCGAGACTCCGTCTCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGAGTGCTCTTGTTGGAAAAGAGCTGT
TTGACCTGTGTGGGGACTGAATACTTACAGTGTATGAGGGTTCACAGCCCTCTCCCTATAGCCACCTATG
ATTGAACAAGCAATGGTTGGTGTTAGGCATCTTCCAGACATTTATATTGACTTCCCTTTACAAAAAATAT
ACGAAAGGTACATGCATAGATTTTTAAAGGAAAAGCAATCAAAGAGATTGTGTGAAGGGGAAATGGGCTT
TGTTGATATGTGGGATGTACAAGAGGGCATGGAGGGAGAGGTGCTCAAGGAACCAAGGTGGTGAAGGCTG
TAGATGAGAGACATTGTGTATAAGGCAGGAGAATAAAAGGCCCCTGGAGGTTTGAAGGTACCAGAGAATA
AGAAGGATCCAGCCTGGTTAGTACAATTGGCTGTGAGCTAAGCAATTGAAGTCTCTTACATGTTGTGAGT
AAAAGTCTTAATTTTGGTTTCAACCATGCCTTTCCCAATATTATAGCTCCAAAACTAGACCATATACATT
CCAGTTTGTAGGTATTACACATGGCATTAATTATTTGAAAAGGGATAATGTATTTAAAATGGTGACATCA
AAGCAAAGGACTTTCAGAGAGTGGCTTTAAGTAGCACCTTCTCTCCCAACAACCCCATATACTTGCTCAT
CTGGTCCCACCCTACTCCAACAATTAAATGCCAAACAAAGGTATATGATCCCAAAGTGTCTTCCAAACTC
CCCAACTCAGTACTGTGACACTTCAATCCTTTATATACATGGTGGGGAAATTTTAAAGCTTTAGAACTCC
CATTGCAGAGAGGAGAGGAAAGACACCTTACTCTGCATTTGGTTAAAGGTAGCTCTTTTATAACATTGAG

FIGURE 3 (continued)

CTTCAACATTTGATCATGGCCTTACGTATTAGTCCATTCTCACGCTGCTATAAAGAACTGCCTGAGACTG
TGTAATTTATAAAGGAAAGAGGTTTAATTGACTCACAGTTTCACAGGGATGGAGAGGCCTCAGGAAACTT
ACAATCATGGTGGAAGGGGAAGAAAACACGTCCTATTTCACATGACGGCGGGAAGGAGAAGTGCCGAGTA
AAGCGGAGAAAGCCCCTTATAAAACCATCAGATCTCATGAGAACTCACTATTATGAGAACAGCATGAGGG
TAACCGCCCCCATGATTCAACCACCTCCCACCAGGTCTCTCTCACAACATGTGGGGATTATCAATTCAAG
ATGAGATTTGGGTGGGGACACAGTCAAACCATATCGGCCTATATTATTTTGTTTCCTGTGTTTTCTCTTC
ACCCTTTTCTCACTTGTGTGAATTTTTGGTTCTTCCCCACCAGGACTAAAACTGTGCTCTATAAACTGTA
AATACTCAGCCTTATAAACATTAATGATGACACAGAAAAGAGAGGTGTCGAGTGAATAATTGGATGCTGA
AGGTTAACCATTTAGTGAGTTGAAAACATCGACAATTGGCCACTCCATAAGAAAGTATTTCCTTAAAGCT
TATTTTATTAGCGAGGGAGACTATATGCATTATGTTATTTTCTTTTCTCAAGGTCTGTATTTATCCCAAA
ACATTCAGTGTTAAAACTATATCAATGCTAGAGTTCAAATCTCAGCTCTACAAGATGTTGACTTTGGGGA
AATCACTTAATTGGCTCCTCAGCTGTCAAAGGAGATAAGGACAGTCACCTCCTTGACGTATTATTGCAAG
AATTTTGTGAGATGATATTTCTCTAGCAGTGTTCTTAACTAGGTCAAACTTGAAATTTGAATAAATCTGG
CATGTACAGTTAAGTATTTATTATGGGCAAGGATTTACTCCAGAGAGAGAAGAGCTGAAGAATACCATGG
GAAATAAATTTGAATTGTTTCATGATGGTAGTGCCCAGATTTCACCATAATGTATGAGAACAGACAGAAA
CATAGGACAAATTTGAAGTTTTTCTGCAGGACAACAGGGAAGGAAGTTTGGCACCAGAAATCTGGGGGAA
TAGGTGCTAAAAATGTGTAAACTAGAAGAGTTGTCTCAGAACTTTTGGGATCCATCAGTTCTGCTGCAAT
GACACTTTCAATAAATGAAACACTGTGCAACAGAGGGGTGGATTCTTTCCTTACCAGTGCAACCAAAGTG
GGCAGCTATGAGAACGGGATCATGAGAGCCTGGGAAACAACCCCTAAGAATTCTCATAGATAATAGAATA
GAAGAAACCTTGAAAATGAGCCTGTGTTCCCATAGGCACATGAGATAGAAAAGGCATATATAGTAAGGTA
ACCTCATTTGTATGTTCACAGTCAGTGAAGGACTGGATGAATACAGGTCTCAAGTGAAATACACTAAGCA
CAAAGCCTGGTGTATAGTAGGTCCTCAATAATAAATGTTTGTTCTCTTTCCCTTGAAAGACAGACCTCTT
AATTAAGACATCCTCGAAAGAGATTTCTCAACTTTTTCATTAGCATCCTCTGGATACCTTCACTCTCATT
ACCTTCAGCACTATGATTAGCGTCAAAAAGAATTCTTCATGTAAAGAGTCTGTAATTAGGATACCAGGGA
GAGCTCAGCATCTGAAAAGGACTGCAGCACCTGCCTATTGTCTCAGTTGCTTTTTATCTCTCTAGGCCTG
CAATATCAAAAGCACCCAGTACAAATTAAAGATGCAAAAACCTGGCTGGTCTCAAAGTTGGTTCATTTCC
CGTTAGAAATACTGGCTGTGCATTTTTCTTGAAATTAGAACTTCAGAACAGCACATCCAGTAATTAGTGC
ATGATTTTCTTTTCACTTGAATGTTTTCTGCTTCTTTTTTACTATTGCAGCAATTGGGTATTTGAGAGAG
AAAAATAATGTCTCAACGCATGCTTCATTTCCCAAAGCAGGGGGCAGAGTCCAGATTCCTGATGAAAGCT
TCAACCTTTTAATTCAGATGAAGTGAAGCTCAATTTATTTTGTTGGAAAGTTTGAACTGGTCTGTGAGGC
AGTTCAACAGTTCAGGCTTACTGTAATTAACTGTCAAATAAGAGTCCGGGACTAAGCAGAGAAACGCAAG
TGGGTCAGCATCAGAAGGGTTTAAATTCTGATGAAATTTTACAAGAAGAATGGCCTTTCGTGGAAACATT
CATCCCAGTCAATAGTTCACTGTATAAGCAGCAGCAAGTGTAGGTGGTTATCAAAAACACAGCTTGAACT
CCCATTAGGCTTCCAGTGCCCTCCCTTTCTGGTTATCACTGATGCTCCTTTACTAGAAACATTAATTCAG
GGTTTCTGGTAACCTTGCCTCTGATAAACTCTTCTACTGGAGCTTGTCCGCATAAGGAGAGCGAGCCTTT
GAGGCTGCGGAAGTTTGAGGGGAATACCTAGAAAACTCCTATTGCTATTATGCTAACCCACAGACTGCAT
TGAATGGCAAAATGCGTAAGAAAAATGTCCTTGGCCGAATGCAGTGGCTGACACCTGTAATCCCAGCACT
TTGGGAGGCCTAGATAGACAGATCACTTGAGGACAGGAGTTCGAGACCAGCCTGGCCAACATGGTGAAAC
CCATCTCTACTAAAAATACAAAAAATTAGCCAGGCATGGTGGCACATGCCTGCAATGCTAGCTACTCGGG
AGGCTGAGGCACAAGAATTGCTTGAACCAGCGGGGGTGGAGGTTGCATTGAGCCAAGATTGCACCACTGC
ACTCCAGCCTGGATGAAGGAGTGAGACTCTACCTCAAAAAAAAAAAAAAAAAAAGAAAAGAAAAAGAAAAA
TGTCCTATATTGTTACCTATGTGGTTACCTTCCAGTGTCTTCATGTAAGTCCAGATTCCATTTAGTATTG
CTTTCCTCCTGCTTGGAGGCCTTCCTTTCACATTTCTTGTACTGTAGGTCAGCTGGTGATAAATATTTTC
AATTTTTGTATGTCTGAAAAACTTCAAACAGAATATGGAAATGACAGACCACCAACACTGAGCAGAAAAT
ATTAGAATTTAATGTAGGCAAATTTAATCTGCAACGCTTTCCAAGACCAAAGCCTTTCATTTAGAACCTT
CATATTAAAGGAAAGCCATTTTGGGAGAAAGTAAATGGCATGACCTTTGTGACAATTTTCATAAAAATCA
ATTTTTAAGGTCTCCATTGAGCTAACATAAAACAAATCTGCTTTTGACCCATATACTGCATTAATAACAT
CCAAAAAAGGCTCTATATCTGAAGTAGTTTTCTGGGGTAAAAGAATGTATAAACAAAAAGAGACAACCTT
TCAAAGAAGAACTCTAGATATGAAACAGGAAAAAACTGATGTGTTTATCTGAAGCAGGCTTGTAATACTA
TGGCCCCAAGTCCACAGAAATCAACTCGGCCTCATGTCACCTTCCCAGTGAACCTTCAGGACTGAGCTTT
CAGTTTTCTTAAACAAACTCACATGCACATGTACATATGTGTGCACACATGCTCACACACACACCCCACA
TAGGCAGAATAATGTTAATAGAGCTTTGCTTACAGATCCCCAGAAGAGAAAAATCAATTTCTATCTTATT
TCTTACTTTTAAAAAGCTGACCTACATGGCTTTAACATTCCCTTCAGCTTGGCTAAACTTTAGACAGGTT

FIGURE 3 (continued)

TGTTCCTAACTATAGGTCCCTGACCTCTTTTTTTTTTCATAGAACATTTGCTTTAGAAAACATGCATTGT
AAGTCCTTTCTCTGCCCGTTTGAGAAATAAATCTGATGTGGGAGCCATCCCTTTGAAATGTGATCATAAA
GATAGTACCCCTATCTCCCAGTCTCTGTGGAAAGTTCAGAACCTAACTTCAATCAGTGACAATCAGCAAA
CACAGATGGCCTAATCACACTGACCAGCCTCTGCCTTACTATCCTGCAGTGCTTTCTCACTAGCTCACCT
CAGGGATTACAAGCTCTCCTGCCTTTTGTTTCAGTGCAGTTGAGTTCCATCTCTCTCCTTCATTGCAATA
GTCCTGAATAAGTCGAATAAGTCTTCCTTGCCATTTTTCACAAGTATCCAGTGCAATTTCTCTTTGGCAA
AGCCCATACATGTATTTTCCAGTAAAAAGATAATGTGAACCCAAGTACCTGACAGTTTCTATAATTTCCA
TCCTATTTCTTAGAAATCACCGAATTAAATGAAAAAAATGTGGAAACAATTAAAGTTCTTTGCAAATCTA
TCAGGTACTTTATCTAGATTCTGCTTGTCTTGCAAACTCTGACTACTTCTGTAAGTACATAAGAAAGACT
TAAATCACACACTAGTTCCCTAGAGTGATGGGTATAATTTTATGGAGTATATAGAAGCTAGAAGGGACCT
AGATGTTCATTTAATCCAGAATTCAAGAGCCAAAGTCATCTCAGAGATGTTTTGTTTGCTCATTACAATG
TTAGAAGATGAAAAGAAGAGGATTGAAATGCTTCTGGTGGGACACGCCGTCCGGTTTATCCCAGAAAATG
CCCTATTTTCTTATACTTGGCTGCTCCCCAGACCATATTTACCGTCTTTCCTTATCCATGAAAACCTTTG
GGGTTGTTATGCTTAAACCCTCATTTTACTTTTTAAATGAAGTTATATGCTCACGGAAGTAAAATAATTT
TGCTCCCAGTCTTGATAAGTAGAAACTGAATTCAGTATTCCAGAAGTGCCAGTGCAATACTTCTCAACCT
TGATTGGATATCAGAATCACCTGAAGAGCCTTTTAAAAATATCTACACCTGAGACTTACCCACAGCATTC
TAAGTACACCGGTCTTGGATGGGGCCTTCGAATTGGCCATTTCCGGTGTGCAGCTAAGACGAAAACCCAT
TGACACAATATATTACCAGACTGTCTTGGAGATTCTGTTTCAGAATGTAGACTGGGAGAAAGTTGCTCTC
AATAAATAAATTTTTCATTATTTTGATAAATTTTTCATTACTATAGGTACTAAAGAGATTAAAACATTCA
ATGATTTTATTAAGAATTCTATGCCAATAAGTTCAGTTAGATAAAATTGACAAATTCCTCCAAAAAACAA
TATCAAAACATCACACAAAATTGTGAATATGAATAATCCTCTCATTAATAAAGAAATGAAATTTTTCATT
AAAGCCTTTATGTGTGTGTGCACAGACCATAAACACCCTACATGCTATAAAACTATACAATCTTGGAAAA
ATAATAAAATCCAATATTATTGATGGTTTTAAAAAATGATCTCCACTAACAATAGAAGGGAAGTACCTAA
ACGTGATAAAAAGTATCCTTAAAAAATATTGAAAGCTTTTTCTCTGTTACTGGGTGCAAAAAAACCAAAA
TGTTTACCTACATGCATCACTGAGGTTCAATAAGCACTGGAGATTCTATTCGGTTGGTACAAAACTAATT
GCAGTTTTTGCCTTTTTATTTTATGGCAAAAATCACAATTACTTTTGCATCAACCTAGTAAGTAACCCAG
TAAGGCAAAATAAAACTGCATCAATAGCTATATATAAAACAAAAGTTTTAAAGACTTTTTTTTTTTTTTT
GAGACAGAGTCTCGCTCTGTCGCCCAGGCTGGAGTGCAGTGGCACAATCTCCGCTCACTGCAAGCTCCGT
CTCCCAGGTTCACGCCATTCTCCTGCCTCAGCCTCCTGAGCAGCTGGGACTACAGGCGCCCACCACCACG
CCTGGCTAATTTTTTGTATTTTTAGTAGAGACGGGGTTTCACCGTGTTAGCCAGGATGGTCCGGATCTCC
TGACCTCGTGATCCGCCCACCTCGGCCTCCCAAAGGGCTGGGATTACAGACGTGAGCCATCGCGCCCAGC
CCAAAAGCTATAAAGATTTTCAAAGAAAATATTGAAATGAATTGTAGTTGTATATACCAGCAAGAAACAA
AATGAAATTTTAGAACCACTTTCAAAAGTATTAAAAATACTAAATGTAAAGGAATAAACCTAAAAAAAAT
GCAAGGCCTTTATGTAGGAACCTATGAAATGTTGCTAAGATAAATGAAAGAATATTTGAATAGAGATATT
TATCAAGCCTATGCATTAAAAACTCAATATGTAATATGTCAATTGTAATACGTCAGTTCTCTACAAACTG
AGCTATAGGGTCAAGGAATTCTAACCACAATCCCAATTAGAGAGTGAATTTGACAAGTGGATTATACAAT
TTATATGAATATTCAAAGGGCCAAGAATATTCATGACACCTTTGAAAAGGACAAGATGTCAAGATTTTAT
CTAGGTTATGACATCTTATAATAAAACTACAGTAATGAAGATATTGCAATATTAGCATAAGGATAGAGAA
TATGCCCATGGAGGAAGATAAGAGTGTGAAAATATATGATGCATATATAAACATTTAATTTTTAATAGG
TGGCATTGCACACGCATGGGATAATAGTGGTCTTTATTAATAGTTCTGGGACATTTTTGGTATGCATCAG
GAAAAAATAATGAAGCTAAACTCCTATATCACACTATTCATAAAAACTCCAATTAGATTATGGAAATATA
TGTGAAAAGCAAATCAAAATGTTTTCTTAGAAAATAATGCCAGAGAATATTCTCATGAATTTAGGATAAG
GGCAGTTTATTTATAATTGAAATGCACAGAGCAATCATCATGAGCACATTAAAATTAAGAAATCATGCTT
ATCAAATAAATAGCATCAAGAACGTGAAAAGGCAAGCCATACAAAGATAAAAGATGTTTGCTAAATATAT
GTCCAGCAAAAGATTAGTGGGTGCCAGAGGTCAGAAAACCTTTTCTGTAAAAGGCCAGATAGTAAATAAT
TCAGACTTTGCAAGCCATACAGCTTCTGTCTCAACTACTAAACTCTGCCCTTGTAGCATGGAAGTAAGTG
TGGCTGAGTTTTAATAACACTGCATTCACCAAAATATGGCAAATCAGATTTGGCCCATAGTCCAGAGTTT
ACCCATTATTGGTGTATAGAATATATAAAAGGTTGCTTCAAAACAATTAAAAAACAATTAAAAGACTGGC
AACCCAAAATAAAGAAGAAAGACAGGAAGGAAGGCTCTTAAACAGTGTTAATCACCAGATAAATGTTAAC
TAAAATCATAGGAAATATTATTTTATACCCTCCCCATAACTAAAATTAGAATGAAAATACCAAGTGTTGC
CAAGGATTTAGAGTAAGCAAGCAGAACTGAGGAGTAACGTACTGATGTTGAGAGTGTAAATTAGTACCAC
TACTTTAGAAAGTTCATTGGCATTATTGACTAAGATACATAAACCTCACAACCCTTCAACTCCACACCAA
GATATACCACAAAGAAATGAATGCATGCATGTTCCCAGGACATGGGTTCACAGCATCCTTGTTCATAGGA

FIGURE 3 (continued)

GCCCAAAGCAAAAGCAGCCCAAATGTCCATCAGTCGTGTAGATAAACAAACACTGGCATATCATTTAATG
GAATGCTTCATCGTAATTAACACATTACAGCTATTTTGCAACAATGTACACTGATCTCACAAACATGATA
TTGGATAAAAGAAGCCAGTCAAAAATAATATTTGCTTTATGTTTCCATTTAAATACATTTCAAAACTAAA
TCAAATTTCAATCGTGTTTGGGAAGGCACACTTAGTAAAGGTAGGAAGAAAACGTATGAAGACAAGCAAG
GAAATGATTAGCATGGAAGTCAAGATAATGGTTAACTTTGAAGGGAAGGGAGGAATTTGGATTGGAAAGG
GTGCACGGGGGTTCTGGATACTGTCAACTCTATACTTCCTCATCTGCATGATACATACATGAGTGTCAGC
TTTATAAGTCATTTATCTGTGACCTTACATTTTACACAGTTTCCTGTATACACTAAAAAGACAGTTTAGA
ATAAAGTTCATGTAGTATAATTTCTAATCGTGTAAATATATAAAGATAGAATGGTATTTATGGAGCATTA
AAATGTCTATTAAAAAGAAGTGCCAAAATATATTAACAGGGAGATTATTCATCAATAATAGGATTTGATG
TAATTAAAAATAACTTATATTTGCTTATGTTTTTATGTTTTCTACTCTGATCTTGGATTGCTTAGATTAT
ATAAAACAATAATAATGAGAAAAATATTTCCCCAAGTGAAATGCACATATCTACCTTCTGCTTGAATAAA
AGCTAGGTGGTATTGTAATTAACAGTATTTAAATATAATTTCACCCAAAGGAGTCTTAAGTTCTGATCTT
GTTTGCTTAGAAATCAAAATGTGAGGAAATGTGGGTAACCGTACTTATCCTTCCTCTACCTTCTCTAGGT
CTTTCTTTTCTCTACAACAAGCATAAACATGCATATGTGGGTTGAACAAAATAAACTGGGTTTTCCCAGA
GTGTGGCCCACTATATGTGAATATTTTAAGTCCTGTGCATATCACACACACCCACGCGTGCGTGCACGCA
CGCACACGCACACACAGAGTATGGTGCTTCAAAGAGTTAATGCACACATATTTCGTGTAGAATTTGCAGA
CGTGTGATCTGAAGTGCACCCTCATGAATCCAATGCCCTCCTGAGGAATAATTTGAACAGAGGAAGAGTT
CCTCTATACAGTAAGGTACTTGGACTTCCTATGAATTCAAATACACTGAGGTCGAAGTGACTTTGTAAAA
AGTATCTGAGGCAGCTCTTAGTGCCTCTGGGAAAACTCAGTCTAATAATACGTGTTGAATATTTTTACAT
CTTTATACAGTTTATAATATCTTTGTTTTCCCCAGCCTTTATTATTACTTAGTATACTTCTCTATTCAAT
ACTTACCAAACCCTGAGGCTACCCAATAATAGTGTAATGTTCTTCACTTCAGTCAATGAACTTTAACAGA
AACCAATGCATTTTAACTGAATTTTTGTTTATCTCAAGGAGCACATTTTAATGAAATCAATACATTCTTG
CTGAAAGCCACATGAATCCATTGGAAAGAATACATTGTTACCGAAACCAATATACACTTTTATAATGTCT
GTATGTTTTAGCGTAAGCATAGCCATACATTTTAGCTGTAACCAATATATTTCTGCAGGACTGATACCGA
GAAAGCCTTATTTCATAGTGAAGTCAATTCAGTCTTACAGAAACTAATACTGTATTCCATATTCCTGAGC
CAGCAGTGTCAGGCTAAATGAAGACTATGATTTATATTGCTGAAAAATGTAAATATTTCCAGAAATGACT
TTAAAATAAAAGTGGTTTTGAAAGTATATAAAGTATTTTAATATCTTGATTAGAGTTACAAAAGCAGATG
GAGAAAAGTTTTTGAATGGAAAAGTTAAGAGCCTTGTGTACAATGTGTGTTTCAGTTAAATATGCATAAA
TATATACACTAAAATATATTTATTATTATATTTAGGTGTTAGTTGCTGAATTTTCAAAAACTCCTGTTTA
TTTCATTGAATGCCCAGAAAAAGGATATCCTTCAAGAAAAATCAGATGTTAAAATATTTAGAGATTTCCT
GTCCTAGAAATACCACGTCTTCATCCAACCTAAAAATGACACAAACTCTTAATAGTCTTCCTCTAATTCC
CCTCATCCTTCAAAAATGTGAATAATAATAGAATTATTACTAGTCAAAAACTAATAGAGGAACACCGAAG
GAAAAACATTCAAGCGATGACTCAACAATAAAATGGTCAAAGAAAAATGTTTAAAACAAGTCATACAGAT
TTGTGTATATGTGTGCATGTACGTATGCATGTTTGGTGAATTTGTACTTACCACTGCAAAAGTCTCTTGG
CCTGAATTATGTAATACCATTTTCTACACTGAGATTGGCCTGCTATACTTTGTACTTAGCCCAGACAGAA
ATTCTAAAAGCATTACCTGTTAGAAAACTAACATTTTAAAATTCAAATGTGCTTGTATTTAGAAGTGACT
GGTTATATCCCAAGACATTATCTAATTGGGAGAGTAACCTTGTTGTATAATTTATCCAGAGTTGGAAAAG
CGAGGGCAGTCTGCTTCCCTAGACATCTTTATTTGCCTTTTTAGTTTGCTCTGCTAATGACATTTCCAGA
GGATGAAGAAAATGAAGAAAAAAGTCATACAAGAGAAAGTATAATAAACCCAAAAATATTTTTAAAAGCA
TCTCTCAGGAAAGCATGAATCCTAGTTAAAATTAAAACATTTCTAATATATTTACTTGACATTCATATAA
GCAATATAAAAACACACAAGCCATCTGCTTGACGTTTTTGATTAGGAAAAGTAGATAAAACACCAAAATT
TAAAAGTAACAACATTATTCTTGCTAAATAAATAAATTAGTAAAGGAAAGGAAAAAATATTACACAGAGC
AGATACTAAAGCAAAAAAAATAGGACAGGAAACTTTTTTCTCTTACAAAAGCAATTATTTAAATCACTCA
AAGTTCCTTGGCTTCAAGGCTTCTGTGTAAACTTGCATCCTCTAGCTGTGTCTCTGTCACTGCAAAGATC
CCAACTCCTAAGTAGCTCTTACTTTTCCCCGGGGTTTATTTTTCTTAAAGGGGTACAATTCAAATGCAGC
ATTCTGCTTTAAAGATCAGCCTTGACAATAAATACTTATAACTTTCTAAATTGGGTGTGTGGACTCCAGA
AATGAAGGCAGGCAGTGAGTCTCAAAAGCACTTCTAATACAAGAAACATCACAAAAATAAGTGCTATATT
CTCTTACTTCCCTTTTACAGATCCCTAGTTTTTGTTCAACTGAACAATATTCTGGCTGGGCATGATGGCT
CACGCCTGTAATCCTAGCACTTTGGGAGGCTAAGGCGAGTGGATCACCTGAGGTCAGGAGTTCGAGACCA
GCCTGACCAACATGGTGAAGCCCTGTCTATACTAAATACAAAAAATTAGCTTGGCATGGTGGCACATGAT
TGTAATCCCAACTACTTGGGAGGCTGAGGCAGGAGAATTGCTTGAACCCAGAAGGTGGAGGTTGCAGTGA
GCTGAGACTGCACCATTGCACTCCAGCCTGGGCAACAAGAGTGAAACTCTATGTCAAAAAAAAATTAATA
TTCTGAAGTTTAATCATTTTAGCCTTTGATTCATGCACTTTGCTGTCAAGCTTGTCTGCTACTTGGATGC

FIGURE 3 (continued)

TGGCCTCACTGAAGCCATTTCTAGCATCATTTCATCGGGCCTCGTAACTGTTAAACTGGGCAACTCTGCC
CTCTCCATGTGCCCCGAGCTATTCCACTCAAGCTTGGTCTCTTACCTTCTAGCTTTCAACTTCTGCATCT
GCTGTTTATTCACCCACATTGAAGAAACTCCCATCATTCTTAATCATTGAGCACCACAACATTCCAATCA
TCAAAGAATGGCTTGAAATAGAACCTCCTTCACAAACCCTTCCCAAGGCATGTTACCTTTTTGGGGGGAA
TAAGCTGTAGGCACTTATTATATCCTGTCTTGCACTCACACATTGCTCTTCACATCCATCAAAGTCTCCT
TTCTTTTCATTTCACACCCACTCTGTAACTGGCCTCCTCTGTCCTCACTTCACTGTGTCAAGCAGTCAAG
CAGTCCCTAAGCAGTAGCAACAAACTGCTATAGCTGGTAGGTTGGTGCCCACACTTTCATAAGTTCAAGC
AGAAAGGATGTAATGATTCCAAATGAATTTCAACAGTTTACTGCTCACAGCACAGAAGGCCTGGGTTTCT
TGTTCACATGAGTTCCCCTAACTAGCTTTGCAAGTACCACAGGGGTGAGGTCAGTGCTGCACACACATGG
ATCTGTGTCACAGCTGAGGACTCCAAAATAAGGAGACCTGGATCTTATCTATGGGTCACTGGCCAACCTG
CTAGTCCTCCCCTCCAGGGAGAAACAATTACCTTTATTATCTAGAATGCTCTAGTGATGGGAAGGAGACA
TTATTACGCTGGAATGATTCCAGGAAGAAAAAGATCTGAATCTCTCTGGACGGAAACATTGTCTACAACT
TCCCAAGGTTGTCCAATATGCAAATAACCTTGAGCAAACATCCTTTGCTCAGAAGACACGTGCAAATGCC
AGACCATGGCGAATAATCTCCCTGCATACTCCCATACCCAGCCCAGATCTCACGGCTTATCATGTCAACA
CTTTTCTTGCCAATAGCTGCAGCTCCCTCTACACCCTGCCCTGCCACACACACCTTGCCAACACTGATTA
TCTAGCAGTTTTCCTAGTCACTTTTTCATGGATTTCCTGAGGCAAGGTTAGGAGAAAAACCTTCCCATAG
CAAAGATTGATGGCATCTCAATTTAGTTATCTCCAATTTCAGGTAGACCCTCAAAACTTCTCCACAAGCC
TTTTCTGGTCTTTGATCAGGTTGTTTTCCCCTCCCCACATTGGCTATTTCAAACCCTCATATCTCCTACA
GGCCTTCACAACTCCCTCTAAATCGATGTGCCTCCAACCAAACAAAATTATCTACACCATAGACCCAACC
TAAATGCTCAATCCCTATGTTATCAGGCAGACTTGCTTCTTGTTTTGCCCTAGGTTTATGCTTTAATCTC
CTACGTCCTATTGTGTCCGGAATTGGTGGGTTCTTGGTCTCACTGACTTCAAGAATTAAGCTGTGGACCC
TCACGGTGAGTGTTACAGTTCTTAAAGGCGGCGTGTCCTGAGTTTGTTCCTTCTCATGTTTGGATGTGTT
CCGAGCTTCTTCCTTCTGGTGGGTGCATGGTCTCACTGGCCTCAGGAGTGAAGCTGCAGACCTTTGAGGT
GAGTGTTACAGTTCATAAAGGCAGCGTGGACCCAAAGAGTGAGCAGCAGCAAGATTTATTGCAAACAGTG
AAAGAACAAACCTTCCACAGTGTGAAATGTGACCCGGTTGCCACTGCTGCCTTGGGCAGCCTGCTTTTAC
TTCCTTATCTGGCCCCACCCACATCCTGCTGATTGGCCCATTTTACAGAGAGCTGATTGGTCTGTTTTGC
AGAGAGCTGATTGGTCTGTTTTACAGAGAGCTGATTGGTCCGTTTTGACAGGGTGCTGACTGGTGCATTT
ACAATCCCTGAGCTAGACACCAAAGTTCTCTAAGTCCCCACTAGATTAGCTAGACACAGAGCAGATTGGT
GCATTTACAAACCTTGAGCTAGACACAGGGTGCTGATTGGTGTGTTTACAATCCTTTAGCTAGACATAAA
GGTTGTCCAAGTCCCCACCAGATTAGCCAGATACAGAGTGCTGATTGGTGTGTTTACAAACCTTGAGCTA
GACACAGAGTGCTGATTGGTGTATTTACAATCCCTTAGCTATAGGTAAAGGTTCTCCAAGTCCCCACCCT
ATTAGCCAGATACAGAGTGCTGATTGGTGCATTCACAAACATTAAGCTAGACACAGAGGGCTGATTGGTG
CATTTACAAACCTTGAGGTAGACACAGAGTGCTGATTGGTGTATATACAATCCCTTAGCTAGACATAAAG
TTTCTCCAAGTCCCCACTAGACTCAGGATCCCAGCTGGCTTCACCTAGTGGATCCTGCACCGGGCTGCAG
GTGCAGGCAGAGCTGCCTGCCAGTCCCGTGCCGTGCGCCCTCACTCCTCAGCCCTTGGGCAGTCTATGGG
ACAAGGCGCCGCCGAGTGTGCTCCACGGCACTCGTCGGGGAGGCTTGGGCCGTGCGGTAGCCCACGGGGA
GGGGAGGGGGTGGGGGAGGCTTGGGCATGGCGAGCTGCAGGTCCTGAGCCCTGCCCCACGGGGAGGCAGC
TGAGGCCTGGTGAGAATTTGAGCACAGTGCCAGCACTGCTGGGGGACCCAGCGCACCCTCCACAGCTGCT
GGCCCAGGTGCTAAGCCCCTCACTGCCCCAGGCTGGCAGCTCCGGCTGGCAGCTCCAAGTGCAGGGCCTG
CTGAGCCCATGCCCACAGTGCCCACAAGCCTGTGCAGCCCCAGTTCCCACCCGCACCCCTCCCTCCACAC
CTCCCCACAAGCAGAGGAAGCCAGCTCTGGCCTCGGCCAGCCCAGAGAGGGGCTCCCACAGTGCAGCGGT
GGGCTGAAGGGCTCTTCAAGCGCGGCCAGAGTGGTCGCCGAGGCTGAGGAGGCACCGAGAGTGAGCGAGG
GCTGCCAGCACGCCGTCACCTCTCACTATGGCTGTGTCTCCACCCAAATCTCATCTTGAAGTATAGCTCC
CATCATCCCCACATGTGGTGGGAGGGACCCAATGGGAGGTAATTGAATCATGGGGGCAGGTTTTTCTTAT
GCTGTTCTCATGATACTAAATAAGTCCCATAAGATCTGGTGGTTTTATGAAGGGCAGCTCCCCTGCACGT
GCTGTTTTGCCTGCCGTCATGTAAGACGTGGCTTTGCTTCTCCTTTGCCTTCCACCATGACTGTGAGGTC
TCCCCAGCCATGTGGAATTATGAATTCACTAAAACTCTTTTCTTTATAAATTACCCAGTCTCAGGTATGT
CTTTATTAGCAGCATGAGAACAGACTAATACAATGTCATTCCTTTCCAAGACTTGCTCCATCAAATTTTC
CTCTCCATCCTGCCTCTCCATCTTCTTTATTTCATATTTTCCCTGAAATTCAAGCTGGCTAAATTTCTTT
TTATCTTAAAAATAATCAGTCTTAATTATGTCTCCTGTGCTCTTTATTGATCATCCCACCATCTATCTTT
CTTTCATAGCTAAATTCCTTGGCAAAAATAATATAAACTAACACTTACCTCTCTGCCCGCTGCTTTCACA
CCATACCAACCTGCTTTCCTACAGAAAAATGGCCATCCACTTAGTGGCTGCAATGGACAAAATGTTTTTG
TCCCCCCACCAATTTCATATGTTAAAACCTTAATCCTAAGTGATGATTTTAGGACATGGGGCATTTGGGA

FIGURE 3 (continued)

GGTAATTCGTTTATGAAAACTGAACCCTCATGAATGGGATTAGTGCACTTATAAGAGGCCTGGCCAGATC
CAGTAGCTCACGCCTGTAGTCCCAGCACTTTGGGAGGCTGAGGCAGGTGGATCACTTGAGGTCAGGAGAT
CGAGGCCAACCTGGCCAACATGGGGAAATCCCGTCTCTACTAAAAATACAAAAATTAGTTGGGCGTAGTG
GTGAGCTCCTGTAATCCTAGCTACTCAGGAGGCTGAGGAAGAAGAATGACTTGAACCCAGGAGGCAGAGC
TTGCAGTGAGCTAAGATTGCACCACTGCACTTCAACCTGGGCAACAGAGTGAGATTCCATCTCAAAAAGA
AGAGGCCAGAGGACTAGCTAGTGCTCTTTTTACTGTGTGAGGATACAGGGAGGAGCCAGCATTCTGCAAA
CTGGAAGAAAGCTCCCACCAGAACCCAACTATACTGGCATCCTAATCTCAGGCTTCCAGCTTCAAGAACC
ATGAGAAATAAATGTCTGTTTCTAAGCAACCCAGTCCGTAGTAATTTGTTATAGAATTCTGAGCTAAGAC
AATGGCCAAATCAAACATACTTTTCAGTCCATTTCCTACATTTCCCTTCTGTGGTATGACATGCTGTTGA
TCTCCACGTCTTTGAAATCACTTCTCCACCACTACACTATAAGCTCCTTAAGAGAGAAACCATGTCTTCT
TCATCTTTATGTACTCAGTCCCCCACAGAGTCAACGCACATAAAAATGGCTAAATAAATGATTTTTTTTG
CACCGATTATCTCCCTTCGTATTGGCGCTTTCTCTTTTACTCCATTAGTTTACCATCCTTTACCTTCCCT
TTAAAAGCTGGAGTTCACCCATGACCTCTCCTCTTCCTTGCTCTGAAGCCGGAAGACTGACTCCCTAACT
AAATTGCTTATTATGCCACAAAACTTTTTCTCTTTTGCAGGCATCCATGGATTTCTGATCATTACTGGAC
TTACCAATCTATATGTAACATAACCCCTGACATTCAACATGTTTAAAATTCAACTCATTATTCCTACCCA
CCTTAAAACCTCCTCAATTCTTAGTGTTCCCAAACGTAGTAGTACCACCCTATGCTCAGTCATTCGAGCC
AGAATTATGAGACACATGCGCCATATATGTACTTTCAGGGGGTCTCTTTTGATTTAATCTAGCCAGCAAC
CCTCCAGCCAGTCCCATTTCTACTGCATGTGACTGTCTTAGTTGAATCCCTTGTAATTTCTCACCTAAAA
TATTGCAACTGCTCTTCCTGTTCTTACCTGTTCTCCCCTGTTCTCCACACGGCTACTAAAGTGATTATTT
GGCAAGTCAAACCTAACTGGGTCAACACTCAGCTTTAACTTCTCCCCATTGCTTAGAGAATAAAGTGTAA
GCTCCTTAGCAAGGCATACCCAGTCCTATTCATGGCCTCAGTCTGCCTATTCTTCTAGCATTGTTCCCTG
TTCATTCTACAAAGTCGTTCTGTGCAAAGGCTCATTAAAGCATGTGCTTGTTCTCTCATGCAAGGAACTT
TTGCTCTCCTATTCGCTTCATTTGCAAGTCTCCCTACCCTTGACTGTACAGTGAACTCCTACTCATACGC
CACCTCAAAATGAGCATCATCCTCTCCTCTGTGAATGGACCACAAGGCATTTAGAAGCTCCCTTCACCCT
GATGGATATTATGGTGTAGATATCCCTACATCACAGCAATCATTACATTGTTTTATAGCTATTAATATTT
CTTCACATCCTTCATGATCTATGATCTTTGAAGGAAAGTGTATTTGTCTTTTATATCTTTGTATGAGAAG
TAGTACCATACAGTGTAACATCTTTTGAGCCAAACACATCAGACATTGGCTGAATGTTCTGCAAATATAT
CTGAACGTTTGTATTAGAGATTTAATTTCTCTAGTCCTTTGTTTTTTAACTTAAAATGGAGGTAAAACAA
AATGGAGAATGCTTGATACAGTACCAGGCACATAAAGGCTCTCAATAAATGATAGATGCTGTCATTAGTG
GCATCACCATTACCATTATTATCATTATTATTATTACTAATGATTTCCACTGTTCTTCTCAAAGCCTGGT
ACTCCTCAGGTAATCATTAAGTGTTTTCTGAATAAATAATTTATAATTATTAAATATATATATATGATTA
CCTTAAATGGTTATCTTGTTGACATTGACTCAGTTATTTGCTATTGTTCCTCCAATAACTTCTAAAGTGA
TCTTTTCAAGTAGATATTTATTAAATATTTATTGACTGAATTTCTCAGTGATCTTTTGCTTCTGTGGACA
AAGAAAGAATAATTATTTCATTTCTTTTTTTTGGGTATATATATATATATATATATATGCTTTATGTACT
ACCGTCATTTACAATTTTATAGAAAATAATGAATGTATAGAGTTTATATTTGGATTCAACTAAAATTTGC
TTGCTATTTAAAAGACTGTCAATAGAAATTAAAGTTAGGGCTTTTGAAAATAAGCCTGATTTAATATACT
TAAGCCTCATGACCAGTTTTTAAAACTCTTGAGAAACAACTTGGAAATATCATATATTATGCACAGCCTA
AGATTAAAGCACCCATGTTTCTCTCTCGAACTCTTCTGGAATGTAAAGCATTCAAGATTTATTGATAAAA
AAGTAAGTGGGGCCAGGTGTGGTGGCTCACATCTGTAATCCCAGTACTTTGGGAGACTGAGGAGGCTGGA
TCACTTGAGGTCAGGTGTTCGAGACCAACTGGCCAACATGGTGAAACCCCATCTCCACTAAAAATACAAA
AACTTAGCTGGGTGTGGTGGTGCACAACTGTAATCCCAGTTACTTGGGAGATTGAGGCAGGAAAATCACT
TAATCCCGGGAGGCAGAGGTTGCACTGAGCTGAGATTGCATCACTGCACTCCAACCTAGGTAACACAGTG
AGACACCATCTCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGGAAGTGGCATGTTTGTAGATTTAGTT
AATTAATGTTAATTAAGCAAAAGATTGTAAGAAACCCTAGTGTGGTAACATAGCTTTGCTTTTTGTAGAT
ATCCTGATGTGACTATAATGCTGTCTAGGACGCTGGAGAAACATCCTCCAAGTCAACATCCTCCTGTGGT
CCTGTTGGCACCCTCCAGTGATGCTGGGTAGCCAGTGTTGTGTTGGCACTTGGTATGGCTGCTCTGGGTA
ATGATGATGATGACTTCATATATGAGTGTCAATTGCCTCATACTCCATATTGTCAGACATTTTGCAAAAT
GTTCTTTGTTAAACACATTACAAATGCCTATTTTGACCACAGAGTTTCTGAGTAAAGCCAATCAAAAAAC
TACCAAAAGACTGCTAACTTCAACAAAACTATTACAAACTTCAATGGCTGGAAAGACATTGAGACCAACA
GTTTCAATCCCACCCTTTCCAAGGGAAACTTTTAAAGCCTTCATATCCTTCTAACTCACGAGACATCATC
CCAGTAATGGACAAGAGTTAGAAACACAAACTTGACTGACTGCCTTTCACCAGAAAGAATATTCAAAAAT
TAGAGGAATATGACTATCAAAAACATTTACAAAGTATATAGCTATTACTTGAAAGCTATATCTATATATT
TTTTTTCCTTATTTTACTATACATAAGAAAAAGACCCTTTATCTCTGTGGCTACTTTCTGACATATTTCT

FIGURE 3 (continued)

CACCGAACTATAACCTAAAAGACTCCTGAAAAGGAGATTTTTGCATGTGGCAGTAACACCAGTCCTGTGA
CAGGGAAAGAGCAACCCAGGCTTCTATTCCCTTGTCAGTCATCAGACCACTGTCCATTTCCATACCACAT
GGCCCATACTCTCATCTTTTCACCAAAATGAGCAGCATTCATAATTTCTAAATTTCAAAGATGTATTTTG
TGAACTTTTACTGGAGTTGAGTGCTTTAGAAATAAGGCAAAAGAGTGCTATCGTCAGGGAATTCATCTCA
CCCTATTGATAAAGCTCAGATCCCACCTGTAGTGGGGGTTCTTGAGTTTAAACCATGGTGAAAATGTGTA
CACTGCTGACCTCTGGTGGAGATTTTTATTTTACTCTTTTTTGGTTAACTTGTCTTTGTGAAACAAGGGA
ATTTTACACCAATTACCTTCATAATAGCAAACACAAAAAATATTTTTGAAGTCAATTTAAATACTGTGTG
GGACCTGTCAGATGCACAGATGAAATTGGGACAGATAACCTATCAATTTGCTCGTTGCTTACCTGCTAGT
CACTCATTAACTTAAAAGTACTTTTAGTGTCTCTTAACTCTGCTACAAAAAAGATTGGAAGATTGGATAT
TGATGTATGTCCAGTGTGGCCCATTTAAAACATCTGCCATAACCATTTAAAAGCTGTTAATTCATGTCCA
TTTACCTATCCACACGTCAATTACAGCTAGTGAAATGCATTTGTCAGTTTTTTTCCCCCTTCCCTTCATC
TCTGAAACATTCTAACACAAAACTGTGCTTGCTGGAAAAATCTGGTGATTACTAAATTAATGTTTTATTT
TTGTCTTAGCATGTCTTTTGGAAAAAACACAGTCCTGATTGTCATATTCTTCTTATGCTTAAGTGCAACA
ATTGGAACTCAAGAATAGCCCCATGCTTTGCAGGATATGAAAAATAGTTTGAAGTCCAAAGTTCCACCCT
CCATATCTAATGATGATCAGTGACTCCGTTACAGAAAGTTTTCCCTCAGTAAACCCGGAGGAAGTGGGTA
CTTCTTATATTACAAAGATACAATGGCAATCTGTCTGCATGTGATTTTTTTAAAAAACATGGGACCTCTG
GATTCTAATTTCTAAAGTTTGAGTAACTTTGGACAAGTCACTATCAGTCACTAAATGTCTGCAAATCTTA
GCATAAGAGACACAAAGTTCTTGGAAGTAAAGAGAGGTATTGTGTAGACAGGGACTATCTCTCTGATATA
TGGCCAGAGACAAAAAATGATGAAAAGCCCAGCCCTGGGAAGGTCTGAGGGAAAAACCAAGCAGAAAGAA
CAATACAGAACAAGCTCATTTCTTGGAAGATCAGCAGGTTAGTGGGCCCCAGAATAGAGGGATGGAAATG
ATCAGATGGGACACTGAAGAAGTAAGCAGCTCAGACCACACAGTTCTTATAGACCATACAAAGAATTGGA
ATTTGATTCTAAGTTTAAAATGGGAGCCATTGGAAGGTTGGAAGCAGGAGAATCATGTGATTTGATTTCA
GCTTTTAAATTTTCACTCTGGAGGCAGGGAAGCTGGTCAGGAGACTATTGCAGTAGGACAATATTGCAGA
ACATGAAAGTGGCTTGGTCTTAGCTGCCGTGGCATAATGAATAACCAAGTATGAGGTGCACAGTTAAAAA
CAAATTTGAAATGTGTTTTGAAATGAAATGTGTTTTGAATTAAGTTGCATGCTATGACAAATATTATCAT
TTAATTCTCATTTTTTAGATTACAGAAGCTTAGCATTTTTTTTTTTTTTTAGACGGAGTCTCGCTCTGTC
ACCCAAGCTGGAGTGCAGTGGTGTGATCTCGGGTCACTGCAACCTCTGTCTTCCAGGTTCAAGTGATTCT
CCTGCCTCAGCCTCTCAAGTAGCTGAGACTACAGGTGCGAGCCCCCACACGCGGCTAATTTTTGTATTTT
TATTAGAGACGGGGTTTCATCATGTTGGCCAGGCTGGTCTTGAACTCCTGACCTCAGGTGATCTGCTTGC
CTCAGTCTCCCAAAGTGTTGGGATTACAGGCGTGAGCCACTGCACCCAGCCTGAAGCTTAGATATTAAGT
GATTTGTCCAATGTCACACAACCATTTGGTTGCAGATTTAGAATACAAACCTAGTTGCCGTGGCTTCATA
TCTGTTATACCTGTTACTCTAGAATAACACTTAATAGCACCAACTTAACATTATTATGAGACCATGGGCC
ACTTTTAAGAGTTACAGAATTTTTGAGTTGGTAGGAACTTCAAAGATTATCTCCTTCCACACTCTCGCTT
TACAGATAAGGAAACCAAGGGAAGTTTTGTATGTTTGTTTTTTGTTTTGTTTTTGTTTTTTCCAAGTTAA
CTGACTTTCTAAAGCTTGCTCAACAAGTAACGGACAGGGATGGCAACAAGTTCAAGTATCTTGATTCTTA
GAGGGATGTTATTTCCACAACAGCATAGCAAGTCCATTATTTGGTGCTTTCTATGACAGGAAATAAAGAC
ATATTTTGAAAGTATGGAGAGAATTTTGCCTACTTCACAGTTATATCCAAATTTATCTTGTTCTTCAAAA
TAATGGCATTTGCGGCAACCTGAATGGAATTGGAGACTATCATTCTAAGTGAAGTAACTCAGTAATGGAA
ATCCAAACATATGTTCTCACTCATAAGCAGATGCTAATCCATAAAGACGCAAAGACATAAAAATGATACA
ATGGGCTTTGGGGACTCGGGGGAAAGGGTGAGATGGGGGTAAGGGATAAAAGCCTACAAACTGGGTTACA
GTGTATCCTGCTCGGGCGATGACTGCACCAAAATCTCACAAATTACCACTGAAGAACTTACTCATGTAAC
CAAACACCACCTGTTCCCCAAAAACCTATGGAAATAAATAATAAAATAAAATAAAATAAAATAAAATAGA
GAAGTTGATTTGGCTCACAGAAAAAAATGGATATTTTACATGGTTTCTATGTATATAATTAGACATTTGT
TCCTTAAAAAATAAAGATATTTAAGACACTAAAACAAATAAATAAATTTATCTGGTTCTTTATTAAATAT
CTATTGAACATCTATTTTCGGGCACTATAATAGATTATAAAGATTTCAAAATTAATGTTATAGCCCTCTA
GGAGATTGTAATCAAGTGGGAAAGACAAAAATAATGCAAAAATATATTTCAATATAACATGGTAAAAGCC
AAAACACAGAAATAAAGATAGTCATGAAAACACAGAGAATGGAGCGATAACTAATCGTATCTAGAAGAGT
GAGGAAAGATCCAAAAGTGAAATTTTTTCCAAACCTTGGCCAATAAGCTAGGTGATGATTGGCTTTGATT
TTACCCCACGAGTAATGGATGCTAGGCAGACAAGAATGAGATTTTCCCTCTTCTTGATATTTTCAAGATA
TAAAAAAGGGAGAAAGTATTTCCCAAAAATTAAGGAAGTAGAAGAACTGAGCTTGTCCGTGAAGGCTCTC
CTCTCTGATCATATTGGAAGAAGGTCATAACAACATTCTCAGGTTATGTGATGGTAGCTCATTCTAAATC
TTTATCAAAAAATGCATTACATTTGTGGTTCGCATCTCCAAAGCTGTGTCATTTCACAGCCGCTACATGC
TTTCATGCTATGCATGGAAAAGAAACTCAAGGGTATCCATGGAGCAGTGCTACTATTACTGTTTGGTTTC

FIGURE 3 (continued)

TTTTCTCCATCTACCTCCTCTCCCAGGATAAGCTCACCCTCCTCTCATTACTCCAACCACTATCTACATG
GCTAAATCTCAAATTCATGTCTTCAGGCTAGACCTACCAGAGCAAGAAGGACAATTTCCATGTGGATGGT
GTTGAGGGATGTCTCTTTTTCTTGATTGCAATTTACAAAGCAGATATCCAGAGCTGGTTCAGAAGAAAAA
CCTAGCGGCTGAGTCAGAATGTTCAAAATTAAGAGATTAGATCAAAATAACAAAAAAAAAGTACTAAATG
TAAAATAAAGAGCACTGATGACCTCTGCTTTGTGGATCCCATTATACCACATACAGTCTTCTAATATAAC
ACCAGCCATATTTTACTGGGTTTTCTATTTCACATATGTCTCTTTCTTGTTAGAAAATTAGCTCATTAAG
AGGAAGGAATATCTCTTGCTCATTTTACATTTCTGGTGCTTAGACCAGGGCCTGGTACAGAAGCACTCAA
CAACAACAAAAAAACTACATGAATGAGTAAATAAATTAAAAACCATCCTGAGGTATTTGGGGCCTTCATG
GTATCTATTACATCTTAGCAGAATAATAGAATCTCTGAAGCATAGCAAGAGAGGGTTGTTAAAGCCCTCC
AGGTGTAACCCCACTCATCAAACAACCCTCTTCTTATCTGTGTCATCTGAAGACTTAGGGTGATAGAAGA
CTCACTGTCTTCTAAGGCCATTTACTAATCTTTGAAAGGCTTAAATGAGAAAGTTGTTTGTTTTAACAAG
CTGACAACTCTGGCTTCCTCCCATACATTCTAGCTGCATCCTTAGGGCTTTCAGTGAGTAAATACAATCC
CTCAGAAGATGCTTTGCTATCGATTTGAGAGCCTTGTCTAGGCCATATTTGATTTCAGACTGAACTTGTT
ACAAGCTTTAAGTCTTTTCATTCACAAATCCTAATAAAAGATTATTAAAAAACCAATTGAAATTGCTCAG
CACAGCAATATCGAAGTGATGGGTTCTTTCTTGAGGTCTTACCTTCTTTTAATCAAGAAGAAAGAAAAGA
ACTATAGACTGTTGACAGTAACCATGTGTTATCTACTTTCCGCACACTTCTTTTCTTCATCTAATTTAAT
TCTTCTAATCAAATCATGGTATTATCATTTTCCCTTTACAGGGAAGCTAATAGGCATTGTTTAAAAGCCA
ACTGTTCCTGGTTCAAAGATATAATGACCTACATTTGATGTTATGTTGACTCAACTGAAGGACTGTCATA
AATTAATGTATGAATTTTAAAACTAAATACATTCTTTAAATTGCAGAGAAATTACCTCCCTCTAGGTAGG
TACCATAGATTTTGGAATTAAAGGAATCATGGCTTTATTTCCTGGCTTTACTTCTTCATAGCTAGGTAAC
CTAAAGCAGGCCTCGTAACTTCTCTGGGATTCAGTGTTCTAATTTGTGAAATTATAGTAGTAACATAGAC
TATGTAAGGCTAAAGTGAGGATAAAATGGAATCACATATGTCAAGGTGGCAGCACTATGCCCAGCACATG
ACAGTGGTGATGATGATGAAGAGAACATTGAGATTCAATTAAATTGAAAATATTGCTGCTGGGAGGACCT
TTAACAGTTCCCTAATCAAACTCAAACTGACATCAGATCCAGAGGGAGCAAGGGTTTTATTCAAGATCAT
AGAGCAAGTTAGCTTCCTGCCACCATTCCTAGGTCTACTCTCCTCTCTGCAGTCCAGACAAAGCCCTCCA
GGTCTAGCATTTCCTCGACAGGATAGGACAGAAATGAGCAGCCCAGGCATCCTTGGTGTTCAGCTTTCCT
CTAGCCCGTGTGAGGGGTGCAGGAGAGAGAGAGAGCACAGTCTAGTTCTCTGCACAGGCTCTTTCTCTGG
GGTTTCTTCCCTTCACATTTAATTGCTAAGGACAGTCACATAAAAAATAAATAAATCTTCATTTCTGTGG
GGTCCATCTGCTCCCACCACTCACCTGCACATGAAAGATGCCTGCTCGTGAATGCATCTCAATTTCAAAT
GAACAGTCAAAAAAAATGCTCCCGTCAAGGCTGCCTCACAGTGGGTACAAACCTCTGCAACAGCGCTCCT
CCTGAGGCAGCAAGTTCATCCTGTCCATTAGTGAGGAGGATAAGAAGGGCCTGTCAGGGCTGCCTCCCCA
GGACACAGGGCCCTCGGGCAGACAGATGCGCTGAGTGTGAAAAGAAATTTTCAAAAGCCTTCCTCGCTCC
CAGCCTGGGGCAGAGCAAACAGGGCTGGGACCATCAAAGCCAGCTGCTTGCCTACAGGCTGACACCCCAG
CTACTGGGGTTTAATTTCACATTCTTACTCTCTCCCGCTCCAGTTACTTTTGGTGATTATTTTTATCGTG
GTATATTTGTAAAATTATTTTTCTTGGATCTTCCCTCTAACACCCATGTGCTGTGGTGATACAGGATCAA
AAAGATAGGTTCCTATCTAATCAGGAAAGAGTAAGGAATTATTAAAATTGTCAGGGGAGGGCTAGGGACA
CTGAATTCTATTTCTTAGATGTTTCCACTTTTCATGATCCCTCTGTCCAATTTTTCCAATCTAAAGAGCA
GAGTGATGGGTGCAAATCATTTCTCTATCCTCCCCTCTTTCTTCCCTCAGAAGTGGAGGACAATAATAAG
AGGTGGAGAGGGTGATGTAATTTTAGATTCAAAAGAGGGTGGTTTTTAAGTCTTCATAGCCAGTACTACA
CAGATTGCTGCCATATAATGGAATTCTTCCAAGTATTTTGGGAGGAATCAGCCTTCTGTTCACACGTCAA
CACATATTTGATATTATCAAATTATTTTATAACTTTCAATGTGCTTCCATGTTTATCTCATTTTAAATCT
TACAATGACAGCATCAGATGGGTGTAATTATTCGTTACTTGTTAACAACAGATAAGCCAGAGTATTCAGG
GAAAAGGAAGGAGAACAGTTTGCATCGCTCCATTAAGCCTTGGGACATTGTCAGAATAATTGTCAAATAA
TTCTTTTCAACTAGATTCTCTGTCAAACTGCCTGATACCTGAGCCCAAGGATGGGAGTGAGGGAGGGGAG
TGCAGAGAAGGGAGGAGGAACAAGAACCTGCTTGTGGCCCCCAGCTCACAAAAATGAACTCAACTCCAGA
GGAAGCTAAATGACTAAATGTGATCCTCCTTAGAGCAATTATCACTCAGACCAAGGAGAGACCAGAAATG
GGGAACCGGGGCTTCCAGAGAGTTGATGTCCCCAAGATCATGGCATAAACACTTATGTCGCCATCAAGAT
CCGATCTCATCAGCAACCCTAGCAGGCCTCCCTGTGAGCCAAATCTCCTCAGCCTTTCTAGGAATCAGTT
TTCTCATCTATAATATGAGATGCTTAGACCTCACTGTCTTTCAAATCCTTTTTGACACCAATGTTAAGTG
GTTCTAGGACAAATCACAGCATCTACTCAGAATGTATTATTTTAGAGATTTAAATGGACACATAAGCCGT
AAAGGGAGTTCTTCATGTTGCTTTTCACTAGTCACATTTTTGACTAGCACTGGGGTTAATATCTCAGTTT
TAACCTTTTTTGCACTCCAAGCAGAAAATGCCTTAGATTGGAGGAATGGGTATTATGAGGGGGACTGTCA
CTTTCCACCATCAGCAGCAGATCTGGGGAAGGAGTCACGCATTATTTGCAGAATAATGGACCTTTCTGAT

FIGURE 3 (continued)

TCACACACCCTCTAGTCAGCTGGTCTGCTCACCAGGGAAAGCAGATCAATGCAGATTTGGGAAATCAAGG
AAAAACAAGATGGTGACACTGGAAAGAAAATGAATAAATGACAAGTAAAAAGAGAAAAGAAAGGATATTC
CAATATTGGCACCATGCTTCTCCGCATATGTAATGCCTTCAGTGCACCCTCCAAGAAAGGTATGGATATC
TCTCCTTTACACATAAAAGAACTAAAGTTCAGAGAGTTTATGTCACCTGCCTAAGGCCATTCAGTGAGCA
AATGGGTGAAGTAGAACTTAAAACCAATCTGTCTGACTAAATCCAAAACATCACACTGTGTTCCTGTCAG
TCATAGTCAGCTTTGTAAATTTGTGTTGTGTTGGATAAAATATATGTTAATGGTTATGCTTTGTTTTACA
CTGTAATTCATTAAAATACTTTGCAATTGAAATAAGCTAAAGACCTTGAAGTTTCAAAGTCTACTAAGTA
ACATCATTAACATGGAGGTAGGTGATAAAAATCTTTCCCAAGTTCCATTATAAAATAGACTTCCCTCCTA
ATCACAGGTAGCAAAAATGATCTTAAATCATGTTATACTTTATATTTGGGAGAGTTTTATTATTTTGTAT
TGAATATTTATGGGGTTTTTTAAATTTTCACTTGGGGAGGTGGGCAGTTCCCAGCATCCATTTCTCTTTA
TTTTTCTTATTACACCTATGCCATTTCCAATCTTTAGTGTTACGGTGGACATGTGACCCATGGCCCACCT
ATCAGGACAGAGGATTCACCCATCTATATAGATAGGTTTAGGGATTGGTGTTTGATTCAGTCACGAACAA
TTGGCTGCATACGGCTTTTTCTGAGACTATTGGAAAAGAAGCATGTTCTCAAATCTGTAGACTTTAACCT
GTAAATACATGAGCCCAGAACGGTTAGGGGCCACCAGATAATATCTGAGAATAAAGCTACTCAATGTAAG
GCAGAGCGAAAAAATGGAGAAGCACCCAACTCTGAAAAAATCAATAGCAACGACTGAAACTATCAATTTT
CCTTTTTGCCAGTGTCTGTTTTCTGTTATTAGTGAGTAAAAGAGAACTCACTGGTCCAATTTCATTGTAT
AGTCCAGATTAATAAAGATTTTTAGCAAAGCAGATTTAGTGTGAAGATAAATGAATGTTTTAGCACAAAA
CATCACAATTAAAACCTCATGGATTTTACTTCATCACATAATTTCGTCTCTTTGGTAAGCATCACACAAG
AAAGAAAATGTCAGGAACAACATTATTTTCATTATTTTGCCACTGATAAGTCTTAAGTAATACCAAGGTA
GGAGACTGGCAGGACTTGTTTTCTGGTCACAACCCTGCTGACCAAAACAGGATCTGGTCCACCCAGGATG
ATGTGAAGAAACTGGCAGGAACCAGCAGATCGTGACAAAAGCCATCCCTAGCTGCCCTCACAGCTCATTA
GTGTAAGATACTCTCACCAGCACCATAAGAGTTTACAAATGCCATGACAATGCCCCGAAAGTTACCACCC
CTTTCCATGGCAATGGCCCAGAAGTTACTGACTGCTTTCCCTGAAAGTTCTACATAACCCACTCCTCAAT
TTGCATTAACCCACTCCTTAATTTGCATGTAATTATAAGAGGGTATAAATGAGTATAAACACAGTTGCCA
AGAGCCCATACATTGCCAACTCTGGGTGCACTGACTGTGAGTTAGCCCTGCCCTGCAAGAAGCAGTACCA
TTCCAAAGAAGATTAGGCTTGCCCTTGAATTCTTTCCTGGGTGAAAATAAGAACCCTTCCAGGGTAATCC
CCAATTTTGGGGCTCACCTGTCTTACACCAGTACCACAAAGTGCCAACCTTTTTTACCAATCAGATTAAA
TTTTTCCTCAATTCCCTCTTTGTGAGAATGCCTTTCTTCACTAGGAAATGGGGACCTTCTCTACATTTCT
TCAAATCCAAAGCATCAGTTTGGCTGGTATCCGTCCAAGAAGGGAAAATGAAAAGCGTGTTCAGTGCCTG
AGGATCCTGTGCTCATTGAAGCACATGCTGCTAGCAGTTTTTTCAGGTGTTAGAGTGACTGAAGACCTCA
CTATAATTTCTGGACTGAAAATGGTTTCTCTAGATGCTAGAGAGAAAGAGTGGCCTTTCTTCCTCAGTAT
GATGCTCAAATATTGTCACTCCATGCCCAGATAGGCAGAGCTTCAAATGCCAAAGCATTCTGGAAGCTCA
GTGTCCTTCACTTAGGCACACACAGCCATTCCTTGAGGCATGCCCAAGCTGCCAGGGTGACTGGGCTAGG
GGGAATCTGACCATGAGCCACAGATTGTGTCCAGAGCTAAGCCTTCCCTATGACCATGGAAAGCCAGAGA
GTGCAAGAGAGGGGGAGTTATTAAGGTAAAGAGGTCAGTTCCAGTTACCATCATTGATCAAAGACACAGC
TGGGATTTTCCAGCGACCTGAGGCTGTGAGTGTGTGGGTGGGGGAAGGCTCAGAGGTGCTGAACAATCAA
AAGACCCTCCTTCCCAGTAGTCCCTGATAGACTACCACACATTCTCGTACTAGTCTAACATATATATTTT
TCTAAAGTAATAGGTTTTAGGACTAATTCAAGTTTTTCTTATAACATCCAGAGCAGGATCTATTTTCTGT
GTAGAGTTTGCTTTCTATTTCATTCTACTTTGGTTCTCCCCAGCATTAACCTCTGCATCTTGTACTACTT
TGTTCTTGTCACCAATCACACTTCCCTGTTTTAGAACAGCATTGACATTTTGTGTGTGCACGGTGCATAA
AAGAGTACCTAACCCACTTTCTGCCCTGTGGTATCTCCAGAAATAATACATCTGCCAACCACTCTAAGAT
ATTAATAGCACTCAAAAATGTTTCCCTGTATGCAACTCCAGCCTTGCTATTTATTGTCAGATAGGTATTC
AAAATTTCACAGGCCACACAGTCTTTCCTCACTGTCAGGGAAGGACTGGCCCGCCATGAATTGCTCCGAT
TCTGAATGAGAAGCAGTGAGACCCAAAGCAGCAAGCCCCAGGAACAGGTGACCTTGATCAGAATAATAGA
AAATCCACATGCTATAGAATAGGGCAGGGAAAGCAACTCCTCCACACCAAGGTTCTATTGGGCCCCGAGA
CAAATGCCTCTGCTGTGACATAAACAGTTGTAAAATATCATGCAGAACTTCTAGTTCCACATTTTGGGAG
CACACTGAGAAAGAAGGACATGACAGCCGGGTAGTACCCACCAGTCGGAGGCAATCAGACACCCCGGAGC
GTCAGGAGGAACTGTAGGGCACTGAAAACGGGAAGAAAATGAAAACTTGGGAGGGCTGGGCACACACACG
AGAAAGCGAGGAAGGAAAATGGGTTTCACAAGGAAACCTAGGAGGAGAACTGGCTATCACCCTGGACCCC
ATTTCTCCAGCTGCTGCACGGAAGTGACAGAATGGCAAGAGTGACCTGGGTGACATGCAGGGATGGGTGC
AAAAGCCACCCTCGGTTCAGATGAATGGATCTCGGGTCCCACATGCTGTCAGGACTCTGTGACTCAGTGA
CGAGTGCCCTCAGGATGATGCCTCCCCAAGCAGCTGGCACTGAGGGGTGACTGTGGTGACATGAAAAGGG
GGAGGGAGGGGGGCATGTTTAAGTCACATCAAAAGTTGAGCCTGGGGCTGGGCGCGTGGCTCACGCCTGT

FIGURE 3 (continued)

AATCCCAGAATTTCGGGAGGCGGAGGTGGGCGGATCACTTGAGGTCAGGAGTTCAAAACCAGTCTGGCCA
ACATGGTGAGACCCCCGCCCCTCCATCTCCACTAAAAAAAAAAAAAAAAATAGCTGTGTGTGTGTGTGTGG
TGGTGCAGGCCTGTAATCTTAGCTACTCGGGAGGCTAAGTGGGGCAGGAGACTCGCTTGAACCCAGGAGG
CGGAGGTTGCAGTGAGCCGAGATCGTGCCATTGCACTCCAGCCTGGGTGACTCTGTCAAAAAAAAAAAAA
AAAAAAAAAAAAAGTTGGGCCTGGAAGAGCTGTTGAGTGAATGTGTTGGGAGAATGAGAAGGAAATGAGG
TGTGGCAGGCCTGGCTGACGCCAGGTGGTGGGACACGCCAGTGCCTCCCGTGCTGCCTGAGGGAGAGGCT
CTGGCCCCTGGGAGAAGCGCTAGGCCCGGCTGGGATGTCTGGGGCTGTCCCTGAAAGGAGATAGTAACTG
TTTGGTTTGTTTGTTTGTTTTGTTTTTAGTGTGGGGCGTTTTTTGTTTGTTTTTAGTGAAACTGTCAATT
CTGAGAGAAGCCGTGAGGGAAGCGGAATCTGCTCCTCCAGATGGAAGCGGAGCCGGAGGGACCGCGCGGT
GGGAAGCCAGGGTGGGCACCGCGGGCAGAGGCGGGGGTGAGCTGAACCACCGCAAAAGCGGGAGGAGACC
CGGGCACCTCGTCTGCCGGCCGGTGCACCGGGGGTCTGCCTTTGACTTGAAGCCTAAAAGGGGGTGAATT
TGGGACTCCAAGAGCGGAGATATTTTGTCCAGTCATGCAGGGCGGTCAGCTTAGGCTTGAAATTGGAAGA
CTGGGGCAGGAGGGAGAGTGGCCCCAAACTCCTTACTCATAAGGGATGAGAGTTAAAAATGGACACGGCG
TCAGGATCCCCGTGGCTTAATGCTCATATCCTAGTGAGCCGTCTGTAATGACATTTTTGACGTGGATTAT
GGCAGTGTTACAACCCTGCTCAGAGGCCGCTTACTGAGTACACCTGGGCTTAACGGGCTCTTCCGGAGAC
ATTAATTCAGACGTGAGAATTAGACTCACGTGTTCATCGCTTCCCCGCTTTTCTGCTAACATCAAATGCA
GACTCATGTATTCAGACCCTGCCTTCTACAGCACTCAGACTTAGAAAGTAAACGCATACTTCTGCAGATA
TATAACAATTTAAAATATCTTATTTTACATTTTTTATATTAAAATTCATTTGGATGCAAACATTAAAATT
AACAAATAGAGACAGAAGTGACATGGAACAGCTTAAAATACAAAGATATAAACACTTTTCATCAAGATAA
ACATTGCCTTAGTGAAACTGGCCCGATTGTCCGTCAGAACTAATGTTTACCGGGTTTTTTTTTGAATAAA
CATAAAAATTAAACGTCCCATTCTTAAAACTTGAGAAAGCTGTATCTCCATCTGTCTTACCTAAGTTTCT
TTCTCGGGAAAACAAACATCAGGCCTCCCAGATAGTATCAAGGAGCTGAAACTCACCAGATCTCTGAACA
ATGAGAGGCCAGACCCTTCACCCACCGTGACTCTGAAACAGACCACCTGTTTCCTGTTGAGCAGCCCCTC
TTCCTTATCCCTTCCCAATTTCTTTTCCTACACATAGGTACATTTCTTCCCTACTATATAAAACCCTGAT
TTTCGTTGGTCAGGTGGATGGATTTAAGACTGATCTTCCATCCTCTAGGTCGCAGCACCCAAAGCCTTTT
TCCCTAACAATACTCATTGTCTCAGTGATTGGCTTTTGGTGCAGAAAGCAATGAGACCTCTACCGACGGG
ATCTGTACTGAGCCCCTAGCGTCTGGGTAATATATAATAAGTAACTTCCAAGGAATTAAAATGTCATTGC
TTAGTACCTGATTTTGGAGGGTTGGGGGTCAGTGGCAAGGGAGATTTCTAGTGAGGATACCAGAGTAAAC
CATGTTGGTTTGATTGGCAGTAACATACGTTTAAAATGAGAGCTGAGTGAGCTACAAGCTTCAGCAGCAT
GTTTAACGCATTCTTTATTTACATGTTGTAAATGAAAAGTTACTGCATAACACTTTTTAAAAAGAAAAAA
AAAACTTTTATTCTTGAAATGCCCAATTTTAGTTATGGATCATACTAAGTACAAGCAAAGGCTATTTTAG
CTGTTCTTAAAACCAAATGCAAAATATACTGGAATAATTTAAATCCTGTTATAAACAAAAGAGATAAGAT
ATAATGACAACTCTAAAATAGCAGGAAAAATTAACTCATTTTAAAATTAGTTGTTAGCAGGTATAATGAA
AGAAGATAAATTTAAACAATTAGGAACTGATGAAGACTGTAAAAATTGCTATTTAGAAAGAATAAGTGAG
AAAATGCTTGGGAAACATGGATATATATCAAGCAATAGATCTGAATGACAAATACCCTAGGCTATTAAGG
AAATTAGTCAAGCAACTTAATTAACTTACAATGATTTTTTCAAAGCTCATGGTAGTTTGGATACTGGCAA
CATGGTACCCACCTTCAGTAAAAGGTTAGGAGAAATTAACTCAAATATTACCAGTGGTAATTTTCCCACT
AATCATAGTCATCATTAGTAAAATTATAAGGTTAGAAACTCAGCACAAGATAAAAAGATTATGGCACCAG
AGCCGTAATAACCCTGAGCATGTTAAAATGAAATAAAGCACTCAGTGTGGTGATTCCTCAGGGATCTAGA
ACTAGAAATACCATTTGACCCAGCCGTCCCATTACTGGGTATATACCCAAAGGACTATAAATCATGCTGC
TATAAAGACACATGCACACGTATGTTTACTGCAGCACTATTCACAATAGCAAAGACTTGGAACCAACCCA
AATGTCCAACAATGATAGACTGGATTAAGAAAATGTGACACATATACACCATGGAATACTATACAGCCAT
AAAAAATGATGAGTTCATGTCCTTTGTAGGGACGTGGATGAAATTGGAAATCATCATTCTCAGTAAACTA
TCGCAAGGACAAAAAACCAAACACCGCATATTCTCACTCATAGGTGGGAATTGAACAATGAGAACACATG
GACACAGGAAGGGGAACATCACACTCTGGGGACTGTTGTGGGGTGGGGGGAGGGGGGAGGGATAGCATTA
GGTTATATACCTAATGCTAAATGACGAGTTAATGGGTGCAGCACACCAGCATGACACATGTATACATATG
TAACTAACCTGCACATTGTGCACATGTACCCTAAAACTTAAAGTATAATAATAATAAAATTTAAAAAAAA
GCACACATAACAAAACAATATTCAATATTCCCTCAACATCATTAAGATAGAGGGAAGGAAAATAAAATTT
ACACTGGCTAGTGAATATGTATTTTTTATAATTTTAGAATGTAAGCACTCAAACATTTACTTACCAAATC
ACTCTTAATTTGTTTAGAAGTTCAGCTATGTAAATTGAAATGTGTCCTTGGCAAGGGAAGACTAATCATT
ACCTTCATGTAAAAGAAGTCTCTAGTGAAGGGTCACAATAGTTGACCAGAGAGCTAATTTCCATTAGTGT
ATACCATTCACTAATGATATCAAGACTGAACATTGTGACATTTGGTTATACCTCAATAGTGAGAGCAATT
TTAGGATTTAAAGTTTCATTGCACTGGGAATTTGTGGTTAACATTGGTATGAGTACAAAAAGGGTGTATC

FIGURE 3 (continued)

TAAAACCTCACAGCCAGGGAAAAACAGCTTTAAATAGGAAAATTGGAAACAAGTATTTGAAAGGAAATAA
AATCTTTAATGAAGATAAATGGGTAGATAAAAGCAAGTAATCAGTGGAAGGATATTCCTGAGCAATGCTA
ATGAATTATTCACTAGAATGGAGCCCACGGGCTGCTGGGAGCTGTCCTCTCCCCACTCCACGGTTCCCGG
CAAAGGCAATGACTATACCAGAACTGTCTTCATGCACACTGGGCCAGGCCTTGAGGGGACTCTGACTGTG
GCGGATTTGGGATAACTACCTTAATATTGTTGAAAACGACAGCAGCTAGTATTAACATTCTTGGGCAGAA
TATAAAATAGACACAGACGCCATGGAGGAATAAAGACAGAGCCACCTTGTATAATAGTAAATCACATTCT
TGTGAGGTTTTTGTCAGATTCAAGACTAAGAGTAGCTTTCTTCTCACTTCCAAACAATTAAAGGAAAAAG
ACCATTTCTCTATCAAAAAAAAAAAATCTAAATGTATCGATACCTCTAATATCAGACAAACATTTTAGTT
TCATTGAGTTTCTGTTTTGTTTTTCAGTTGTAAAATACATATGGTTTCCTAAAAGATCTACTTATCAAGA
TGAGTGTAAAGGTTAAATTACCTGAGCTATCCCATGGTAAAGTTGTTCACAGACTTTGAAGTTATATGCA
CCAGTTATCATCCCCATCATTCTCATTAGATCATGTTTGTACAACTCTCCCCCAAAGTATTAACATATAC
ATGGACCATTTAAGAAACATTTACCTCCCAATAGTGTACTACTGTAGTGAGTCAGGAATACGGTGATAAA
TAAAACAGTTCTCTGCCCTGAGAATTTATACTCTTGGGTAGAAGGTGATATTTTAGTGCAATGTGACAAT
GATTCTGATTTTTTTAAAATATGGTTGTACATGGGAAATACACTTATTCCATTCCTGGGTCAAAGAAGTC
TTCCTGGAGGAGGTGATATCTAGGACAAGAACTAAAGGATGTGTAAAACTTAGGAAAGTAAGAGAAGGTT
TTGATGGGCGAGGACAACTAGGCAGAATAAATGACATGTTCAAACACCTGGAAGAGACATTTATACCAGA
TTTTTGGAACTCAGCACAGTTCAGTTTAGGTAAAATTTTAAAATGTCATCCTGTGTTTACAGAGAGATGA
AACTGGAGGGCTTGATAGAAACCACGTTTTCAATGACTTTATACAACCTGCAACAGAATTTGGACTTTTG
CTGGTGGTCAACAGCAGCTGTTAAGGATTTTAAGCAGACCATACTATGATCATATTAGCATTATTAAGGC
TTGTATTGAGGATTTAGAATAAGATTATTGATTACTATAGTAATCAATATTGACCACTGCAGCAATCCAG
ATGAAATATACTAGTAAAATGATCTAAGGGAGAAGGAGTCTGCAAACTTTCACTGCCCATGAAGTTTTAC
TATAACACAGACACATCCATTTCTGTATTATCTGTGGCTGTTTTAGTGAGACAATGACAGAGCCAAGGAG
TCACAGCAGAGACTGGCCTGCAAAGCCTTAAACATTTACTATATGGCACTGACCAGAAACATTGCCACCC
CTTGATCTAAAAAAAAAAATTATAGAGAAGGAGAAAGTATTTCAGAAATATCAAGCAGTTAAAATGAATC
ATTTGTGGCTGGTTAAATGTGGAGTAGGAAGAAAGATAAGTCTAAGATGTCTACTATGGATTGAATGAAC
AGGTGATTAATAAGCTAGATCTGATATGCCTTCTTTAAAAATGCTCAACTAATATGAAATAATCATGCTA
CTTGTGATCGCAGCTTAGTGGAATACAAGTAACAACATACTGCAATGTATTAAACCTACAAAATTGTCAG
TCTATATGGTTCAACACGTAGATGAAATAGGCCACATTTTATCTGGAATCAAAATTGAAATGAAGATTAT
CTTCCAAGTAAAGTTAAACTTGCCCCTTCAAATCTGATTTTTTTTTCTTGAATGACTTCCATACTTGTTT
CTCTGTGCCATTAACTATGCATGTTGGACAAACTCAAGTCTCACTTTTCTCATTTGCAAAATAACTGCTT
TTATTATATCTAATATCTAAAAGTTCAAACATTAATAAATCCAGATAGTATGATTTTCAATTAATTTACA
ACAAAGTAAAAATATAGTTGAGGTGGCTGTAAATTTGAGTAATAAAACGTCAAGAGACAGAACCCTCTTG
TTAGGGAATTATTACTGGGCTTAAAAGGAAGGTTCCAGACTAGATGCTTGGGAGGCATGTATCCAGTCAA
GTCCAAAACTGGACTAGATACACACTATGTTTAGTTAGTTATAACTTTTAAAAGTCAACAAGGTAAAAAT
CTCCTTAATGGCCAACTTTCTGTAATTTCTAATACTTCTGATGCCGTGATGATTCACCTCTATTGAGAAA
CTCAGTGCAATTACTGATTTGTTTGTCTTTCTTTAATATATAGAACCAATCAGTCTGGTTGGCCTGTCAG
TTGACTAATGAGTATATTGGAAAGATTGAGATGGGTCAACTGAAATATATGCCTAAGTCAGCTGCTTTGA
TTTTTGGTGTCTAGAGATACAGCTTTCTGAACGTTCCTTTTGTCCTGCCTTTTTCTTCTCATATCCTGGT
ATAATGAGGGGGAAAGAGAGGATCTTTTGTGGTATCACACATTTGGTTGATTATAAGAACACTATACGTC
ATATAAAAGAAGAAATCGGGAGAACGAAAGTTGTATATATAGTATGTAGTATCAGTGTTGCATTGTCTAT
TACTTCAGTATTTAGGCATTTGTATTTAAGATCGAAAGTATAAATATTGTGAGTCACGATCAATTTTGCT
TTAAATCATTTGGGCAGGTCCAGGGCCCAGGCACATTGGCAGCTAAGGCACCTGTTAAGGGAGATGATAA
ATTGAGTCCTTAAGTCCTTGGCAGAGGAGCTGACTTAGAGATAAGAGATAAGAAAATTAGTTTGCAATAG
AATCTCTAATGATTAGTTGGGATGGAAATCAGAAGGTCTTCTCACAGTCTGATTACATTGTTTTTTATTA
TCTTGGCAACTTATTTGGAACAGCAGCATATTTTGCAACTTTCTCCCCTCAGTCCCTTCAGTAACATATT
TTGGTTGAGTGAACAGTAAATAACAAGAAGAACTAGGGACAATTAACTATTATTGTAGCCCTATGACTAA
TGAAAATCCGTACATTGCACTTTGGGGAAGAATGTACTTATTAACATGCCTGTGGGGGGTAGGTTAATGT
TGCTATTTTAACTTTGCTTGAAAGAAACTAGAGTAACTTACCCAAGGTTATCCAGCTGTCAGAATTACAA
AAGCAGAGTTCTTCCCAGCAAAGGCCCCAAGCCACCTTGTGAAGCAAGTCAGGAATACCTGCAGCACCCT
CTGGCCATGCCCCAGATTCTAAACACAGAATCCATCTCTGCACAATGAAGATCCTTAGTTAGCTAACTGT
TGTACATAGTTACTAGGAAAGCTGAATACTCCCAAAGCTTTTCACATTTTCTTTCTTTCTTTCTTTCTTT
CTTTCTTTCCTTTTCTTTCTTGCTTTCTTTTTTCCTTCCTTCCTTCCTTCCTTTCTTTCTTTCTTTATTT
ATTTATTTCTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTACTTTTTTAGGA

FIGURE 3 (continued)

ATTTTGAACCCAATAAAACCTTCAGGACTGGAAGGAGATAGTTTTAATGGTGAGGTGACAATTGATGAGG
TTGATACGGGAGTTCATGGGCCATCAAATCACACTGTCACTTATCTTTATTAATTCAACTAAAATGTACT
GACCACTTACTGGGTAGATCAGTGTTGCTGTGGCATAAATCTTAACAGCGTAGTGTAGTATTAAACATGG
GGTAGATACTGAAGGCTTTTCTTATATAACGTGAAAGAGAGTGGTTTATCCTATAGCTACTGGTTAGCTA
CTGGAAAGTTGTGAACAGATGTATTGTTCAATTAGATTTCTGTGATTGGTTCTGGCAATAATCTGGAGGA
TGGAGTCGAGGAGAAGTGGGAGCAAGAATGAAGAAGTAACAGCCTTTTTCCAGGAGAGAAATGATGAGGA
CTTGAATTAGAGCACTGGCCCTAGGTACAGAGAGATGAAGACAGATTATGAGATGTATCAGTACACACAG
TACAAGTAGGCAAGGAAGACAGAAGTGACTGGATGCAGGAGGCAAGAGTAAGGAGAAGTCTAAGATGACT
GCTGGGCTTCTGGCTTGGAGAACTGACTGGATGATGGTGCTGTTCAGACAGACTGGAATCACAGGAGGTA
AATCAGATGAAGGCTGTATGGGGTGCAGCAGATGCAGGAATGGAAAATGTCTTTATTTTGAAAGAAAGTT
AAGTGTGAAATGCCTGCAGACATCTGAAGGACAATTTCCAGTAGGCAGTTTTCTATACAGCTCCAGACCT
GAAGATGAAATCTGTACCAGCACAAAGATTGTGACAGTCATGATGTAGTTGGCACTCATGCATCTGGGCC
GCCCTTGATCTTCACCCAGCTGGTGTTTGATCATAAATGGAGGTTAGAATCCTTAGAACTAAAAAAAAAT
GAGAGACATTCATTTTCTCTTTGACTTTGTTTGTTTTTAATATTTTTCTTAAAGCCCTGAAGTATTCTGA
TGATCTTAGCAAGAACCAGGAAAATATGCACTTCAATATCAAGGTGTGTCTAATAAACGTTGGAACGCTT
TCATAAAACCAGAAAAATAGGAAGTGTAATTCATAGATGTTTTCCCTGTATTCCCTTTGTTTCCAATGGT
TTCTCTGAGTATTTTTAATATTTGCCCTCTGCCTCATAAGAGTCGTTAAAATTTATCTGCAAAACAGTAA
ACAAAAGTAAAGAATTAAAATGGTCATAATGATGATGAGACTTTATATGTGTAAATCACTAAACACAATG
TCTTTAGCTCATAATTATTCAATAAATATTTTTTCTACCCACTTTAATAGATCTACATGTTTACAAAATC
TTCTGCAGAATAAAACTAGATGAGTAATATTAATCAAATTACTAGTTGTAAAAAATCAATTCTAAGCATT
CCAATTCACTTTGCATTGATTTGCTCTTGAAAACACTTTTAAGGGTTTCCTTCTGGTTCTTTTGTTTCCA
TTCAAAGCACCAAGAGACTTGCATGCAATAACTGAGGCTTTTTATTTTTAATTACAGAAGATTTGTTTGT
TCAGGAATGTGTCTTCTGAAATAAACCTAAAGTTGATCATTGTTACATTGTGAAAAAATAAAATTAAAAA
CCAAGAATGTTAGCTGAATTCTGATAGATCCATTCCAAGTTAACCTGAAAGTACTTCTTTAAAATAAAAA
AGTTGTCATTTGTCTAGAATATATGAGAAGGAAAGCTCACTCATTCAATTCATACAGGCTAATGGCGACA
CCAAGTGGTATCATATTGGAAATGTTTTTAGTCTGTTTTTGAACTTCTGAAAGAAATTCTAACCTGGGAC
AATTGTGATTGTGACCAGCATGGTTTGTAATGTAGCTCTAAATAGGGTGGAGTTTTAAAATTATTATTAT
AACTAGTATTTCTCTAATAAAATTTTTGTCTCCAGCCAAAATAAGAGTCAAAAAAATTCCATATGCACAG
TCATGATTAGTAGATAAATGAGCAAAAGTCATTTTACTTATCCTTTTTGGAAAGAAGGTAGGAGGCTGAT
GGTGTGCAATGTGATTCAGCACTCTGCAGAGGCTGCTGCTATCTCTAATGATCAGGGTTTCCATAGGGAA
GTTCAATCCAGTGAGTTCAAATCTTTCTTTGCTCCTTATTAGGTGTTTGATTTGGGGTCCATTATCTCAA
ATCTCTCAGTAATAAGTTTTTTTCCATATATAAAATGGAGGGTGATATTAACACATTGGGGCTTTGTGAA
GATTCAACTAGTTCATGTACAGGAAGTATTAATACAGTGCCTAGCATTGTAGAACATACTGAAAAATTGT
GCTTCTTTTTGTTAACTTCATCATCATCATCAAGTCAATCAGATTGACCTATGGATCTCTATACACAAAG
TTTGTCTCTCTTCCTTGATGGAATACAATAAAATTTATACCTGATTCCTACCCTCATAGGAAACGCTTGT
TTTAGAATCAGTATTTTTGTACCTGAGTATTTTTAAAGCAGTTTTAAAATTACACTAGAATTCATATAGA
AAGAAATCATCCTTGGCCTAATCCTGACTCTATTCCTGGAGGTCTATTTGTAACCAAGTCAAGAGAAGAG
CAGGGGAACAGGAAGCTTCTGCTCAAATGTCCTCACGTCACCGAAAAATGGAGTGTGATATAACTGTATT
TACTTTGTAAAATGATGAGCCTAATATCAATTTAAAGAATAGGTTCAGGAAGGGACAGTCTAGTCTTCAG
ACTAAAGCAGTAGAGCTAGTTAGGCCTTGGGAAGAGGGAAAATGTGTGTGGAGCTGTGAACAGACAGGTT
TTTTATTGGCTATGGGAACACCAGAGAGGTGGAAATCAAGGATGATGCTGCTATTTCTCTTTTCATACCT
TGGCAGAAGAAGATCTACAAATCTAGAAGGAAGTGCAAAAACAATTCTCTGTTACTACTTCTAATAATGC
AAATCTTAGGGCTTAGAGCAAGGTTTAGAACATATCATGGAAAATGAGGGATTTGAAACTTCAGCAGCTC
TTCAACAGTGGTCTCACAGTTCCCATTTGTCTTCCATACCCATAATTCAGGACTTCCACCAACAAGATGT
ATGCTCCTGGATGAAATCTGAAAATATTAACTGCTGTCATGTTTAAGGACCTGTGCTTAGTGTTGAGCAA
GCCATATAAACTCTCTGAGTTTCGATTCCATAAAATAAGGGAGGCATTTAGCATATTCCTAAACTGTCTC
CCTATTCAAATATTGAATCTTTGTGACTTTCCCATAAACCGCTTTTTAATCACTGACTTCCCTTAGAATA
AAAAAGTTTATCTCTTCCTCCCATGTTGATTTTTCTCTCTACCTAAACAAAAACAAAAATAAACAAATAA
AAAACAAACAAAAAACAAAAATGAAAAACCTTACTGCAATCTACCCTGCATTGAAGAATTATATCATAGG
TAGGTCCTGGGTTTTATGGAATAAACATAATTTTAAACCTGTTGTCTCCCAAAACACACTTGTGTTGTGC
CCTAATTTGGGATTTGGGAAAAACGGTCTCAGTAGAGATAGCTAGAAAGCTTTCTTTCTGCACCTGCTGA
AAACCATGTGAACCATTGGATAAGCAAAGCCTTTCCCAGATGAAGGACTTGACTGAGCACTTCAGTCACC
AGTGTGCTTCTCAGAAAGGGATACTGGGTCAGCTCTCCCCTCAGCCCTCAGGCCCAGACTCCCAGCCCTC

FIGURE 3 (continued)

TTTCTGGGAAGGAATTGTCAGGTCATGGACACTTTCCAGGGGGGAAAAGTGTCTAGGGTCTGTCTAGTAT
AAATAAGCTTTCTAACATACAGTAGCAGCAAAGCAACTTGAGCCACTGAGCCCTGTGGCAGGCGTTTCCT
CCAAGCCTTGGTTCTCTAATTGAATGTCACTCTTTTTATTAGGAGGAGAAGGAGATTGCCTAGAGACATT
GCTTAACACTTAAGTAGGCTCGCCTAAACCCCTTTCTCTGACACAAGCAGCAGCCCTGGAGAACTGTTAG
CAAAGGGCTTCATTCTAATGAGAGAAACTTCAAAGGCCCCAAATGAGGAAAGAAGTGTCGCTGGAAAATG
TTGAAATGACAAATAGCGGTATTTCCACTGACAAAAGATGAAGATGAAACAAATGTTAGAACAGAAAACA
TGATTTTATTTTGCCATGCTCTCACTGGAAACTATCATCAAAGCCCTTAACTGAAATGAAAAAGGTATCG
ACATAACAAGCACACCAGAGTGAAGTTAGATTTCTAACAACGAAAGTCATCTTTGAAATAAGAAAAGCTT
ACAAAGTAATGAAAAATCTCAATGCAGAAAGGAAAGCATATGGCCCAAAATAGTGTTGTGCTGCGGATTT
GTTAGGAACGTCAAGCTGGAAGCCACTTAGGGATCATCTAGGCAAACCCTTTTATGTTTCAAAGGAGAAT
TTGAGCCCAAAGGATTTTAAGTAACTTGCTCAAGGTCATATAACTAGTTAGTGACTTCGGAATTGTTAGC
AACTGCCTTCCCTACCTCCGTGGAGCCAGTTCCTGAAGTCTATCTACAAATCCACCCTTGCCCGGTTACT
GAGACAGCCCTGGTCAGGGCTGAAGTTGAAGTTCACCAAATGCTGGACCCTGGTATTTGTCCACCCCCAC
AACTGGGCAGGCCGATGCTCTCTGAAGTTAGGTCTGTCTGACACATGACAACAGCCACAGGGACAAAAAC
TTTTTGCCCATTATGCTTCTAGAATATGGTATGTTCTGGAAGAATAATGGGCAAAAAGAATGGAGGGCTG
GCGAAGGCATGGTGCATCCTAAAACCTGGAGCCTACAGAATTAAACATTATAGATAGGAGAAAAGATAAA
AAGGCCCAAAAGGTAAAATTTATTATTTTAAAAAAATGTGCTTAATAGGAGAGGGCCTGAGGCTGACTCA
AGAGGCGAGATATTCAGATTGCTAGCCTTTCAGAAACTGGCTAAAGGATTTGAATCTGGGTAGCTCAATT
TGCCTTCCAGATATACAGGTCTCACATTTTTTCAAGAATAAGTAGGAATTTTTAAAAACGGCATGGAGCC
TGAAGAGATGAACAATCTTCGATCAAAGGAAAAGAAGCAGCATGCAAAATACTCAGAAAAAAGATAATCT
GAAAATGATGTCCCGTAGAATCCAAAGATAATGTGTGGAAACTGTTTGGAATATGCAACAAAAACAAGAT
ATATTATTTATGAAACAGGATGATCACAGTGAAAGGAGTCTGGCATGAAAAGACTGAGAGAGTTGGCATG
AGGAAGGATTGCTGATAGGATGCTCAGCCCACACTCTCTCTTCTGAGGTCTTCAGCGTTCCCAGCCATTC
CCAGGGCCCTTTCATCCATCTAGAATTCTCTCCCAAGCTTCATACCCAGCTATGAGGCTACCTTTGTGAA
ATTTAAATGTATACATTGCAGGAACCTCAATTGTAACAGGTTCAAAATGGAACCCTTGGTCCCCATCTCA
CCCAAAGCCTTCAGCAAGAAAGGCACCTCTTTTCAGTCCTTTGCTTATCCCAAATCCTTGTATAATTTAT
CTGCCCTCACTATTCCCATACCTATCCTGGTACATTCTGTCCAACATGAGAACCTATGATTCCTCCTTGA
AATATGTCTCTAACAATTTCCTTTTCTGCATACACTACTCCACTACTTTCAATTAATATCCCTCATCTCT
TGCCAAGAACTATTAAAATGATATTCTCACTGGGCTTCTTGTTTCTATTTTTGCCTCCTTTTATTTTATT
CTCCATATAGTAGTCCAAATTACCTTTAGACACTGCAAATTTAAGTGTTTCTCTCCTGAACTCAAAACTC
TTTAAAAGGTGCCAATAGCATGAATTATGAATATAAGTCTTTTTCCTGGCCTAACTTAACAACTTTGATG
TTCCAAATCTACCGGCCTCATTAGTTTCTTTTGCTACCATTCCCCTTCTGTTTCATAACTCTGCTTCCAC
ATAGACACTGTTTCTGTTCTCCTTCAATAAGCATCATCTTTCACCATCAGGATTTTGCACATGCTCTTCC
TTCTTTCCGGAACACCTTTCCCCATTAACATAGCCTTACCCAAAATTTAGATCTTAAATGGTACTTTCTC
AAAGAGGGTTTCCCTCACTGCCAATCTAAATATGTCTCCCAGGTTACCTTTTCATGGCATTCTTTGCTTC
CTTTCTTAACACTTAGTTAGGACAGTTAATAATTATATTGTTTTGCATCTCTTTTGCTTATTATTATAAC
CTACACTACCACAATAGGAAATGGCACAAGGAGACAATCCATAAATAGCAATCTGTTGGCATGTGAAATT
AGATAAAGAACATAAGCTTGCCTCCTTTACCTCTAAATATCCTATTGTAATGACTGTAAGAATGGAAAAG
GAAACATACCAAAGAAAATTGGAGAGATAGGAGGGTATTCCATGGTAGCTGGAAGGTTTGGAGATAGGAG
GGTATTCCATGGTAGCTGGAAGGTTTTGGGTTGATTTCCGAAAGTAATAATGTATATGGCTATTGATGGA
TAAATCAGGGTGGAGGAACTTGCTCAGTACACATAAAGAAGAATGCCAGGCACTGGGGGGAATCAGAATT
CTCAGAGAGGCTCATGAGCCAGTGGACACTGACTGGAGCGGGGGGAAGAAAGAGACAGAACCACAATGGA
TCCATGGCTCCCATCTTTCTGTTGGCAGAGTAATCGGCAACCCAGAATTACTCCCTAAAGAAAAAAAAAA
TTGTGAACTTCTTTGGAAAGTAATTCTTAAAAGCTGCCCTGAGAGAAAAGGAGATTTGAATGTGGCTGAT
AGAGCCCAATAGTAGAACTCTTCTAATTCTGAAATTCAAGGGAGTGAAGGCAGAGGAAGGGGAGTGGAAG
TAGCTAGAAGGGGCCACCCCTCCGGGCTTCTTTGCCTGCGCAACATGCAGGTCGACATATTTGTCCATAA
AAAGCAGGCTGCCCAATTAGTCACACTTTCTGAGACACGTGTCCCATGTATTCAGCAGTAGAGATTACGT
AAACCAGCTACCTACCTCAATAATCAAAATTATCATTACTAGATATGAATGGACAATCAAAATTTACAAG
GAGCTGTGGAGAACATCATTAGTTTGCAATGCAAGAACCAAGATTGACACTCAGAAGAGCTGACTCCGAA
AGAAACATTTCAGACAGGAATATTAAAAATTTTGATAGGATTTTTAGCTAACTCAAGAAGTCATTACACA
CACACGCACACACACACACACACACATACATACACAGATATTAAAAAGGAATAACCAAAAGGCAAGATAG
TGTTCGTGAAGTTTAGAACATTGTTGAAAAAAATAAACCAGAAGAGCTACGAGAAAAAGTTCAGAAAATA
TCTCAGGATTTAAGAATGGAAAACAGAAAAGTTGAGATGTAAAAGATCAATTCAGAGGGCCCAGCATTTG

FIGURE 3 (continued)

ATGTGTATACTTTCTAGACAGTAAGATGGGAAGGAAATAAATAATTAAATAAATTGTACCATATTTCATA
AATGCTAAAATGACCTCATCTCTAAAATGCATTATTATTTCACATATTACTAAGGAAATAAAAGCTCTGG
CAATTGAATTATGATGCCACATTTTCATCCACTTGAATTGTTATTTTAAAATATGTAAAGAGTTCTTTTA
GATATGTTCAGACATATATTTTATTATATATTAGTCTTGATCATATATAAAATTAAATATTTGTAAAATA
ATTTCAAAACATATTCAGTCTGACTCTTTTAAATAGTTACGGGTCTTAAGGTCATATATGCTCATTTTTC
ACCCCAATATTGCTTATTGTACCATCAGGAACTTTAGGACATGGGCATTATGAAACACTTCTAACTGTCA
CCAAACATAATACTATTAACTCAGATTTTCTTCCAAGCTTCTGAAACCATTTCTGCAAGTTTTGATGTTG
GCATTATTTCATATGGTATGTATAGTTAATACAATAGCCCAGCTTCCACTTGTAAGGAGGGTGGCTGCCT
TTCTTAGTCCCTATAAAGCATGGGCATTGCTTTGCAAGAAAACAGTAAATTTCACTCATTCATCCAAATA
TAAGTATTTGCTTCCCTAATATCAACTATTGCATCACCATTCCATTTCAGTAATTTTCAGCATTCACAAT
AAATTTTCGACTTCAAATAACAATACATTGTTTCAAAATTAATGGCAGCTCTACTCAACAAATACAGCAC
CAACATGAACTTGCGGTGACAACAATATAGGCACCAATGATGAAATACACACTTGTATGGACACTGATAA
TTACATCAAGATCTTAATTTCAGAAGCATGAAGATATACAAAAATAGATCTTAATATGGGCCTTAAGCAC
AGTGGAATATTCAGCTTTTTATTAAATTTCTATTTTTTATGTTCATCTGTCCAACATTGAAAGAGGCATA
TTAAAGTTTGAATTTTATCTTCACTATGAATCATACCCTTTTCTATACCAAATGACAGCATTTCTGCTTT
TTTATTTATTTCATTGAAGTCTACTTTTTTATATTAATAGCTTGACACCTGATGTCTTTTTGTTTAAATT
TACTTGATACATCTTTGCCTATCATTTCACATTTATATTTCTTGTCACTTTATTTGAGATAAGCTAACTG
AAAACCACATTTGGCAAAACACTGCTGTTCATTTCCAATCTAAAAGATTTTTGTCTTTTAGTAGGGAAAT
TACACTTAGTTTGATTATAAAATTTACATAATTTAGATTCATCTCCCTTAGCTGATTTTAGTTCTTGTCA
CATCATTTTATACCATGATTTCTTCATTCTTTTGTTAAATTTCTTTTTATTGTGAAATATATCATGCTCA
TAAAACAATGTGTGTGTGTATATATACATATATATATATATATGTTAATAGTAAGTTGAATAAACATCTA
ATACCCACTACCCAGCTTAAGAAACAGAAGATCATAAATGACTTTGAAGTTCTTATTGATCTAATGGATC
ACATTCATTCCTTCCCCCAGATTTAATACTATCTTGTATTTTGTGTTAATAATTATTTTTTATGCCTTTG
CCATATATATGCACCTTAAAAAAACATAATGATCAGTTTACCTATTCCTGGATTTTATACAAAGGGAATT
GACACCTGCTATTTTTGCTCTGCATGATGTTTTGTGTTGGTAGCTGTTATTAATTAATTTTCCATAATGT
GTGGTATTCCATCCAAAGCTGTACAACCTCCCAACAGTATTAGTAACATTGTGTTCTATATGAATAGTGC
TGACCATGGGAACAGCGCACCAGAACTGAGCAAGATGATGACTGTGATTCTACTGTATGAGTGCAATATC
ATTTGTTCCTTTGAATAATTCATTATTTATTATTTCTATTTATTTTTCTTGCTATGAGTATGATTTTGCA
TGTCTTCTGAACATATATGCAAGAGCTTCTTTAGGGTTTCTAACTAGGAGTAGAATATCTTAGCTTTACT
AAGTAATGCGAGATCATTTTCCTAAGTGGTTTTACCAATGCCTGTTCCCACCAGCCATGTGCAAGGACTG
TTATTGATGTTTGCCAAGATTTGGTATCAACAGACTTTTAAAATTTAGAGTCCGTTCTCTAATTTCTATT
TTAGTTTGTTTTCTCTTATTAATGAGATTGAACATCTTTTCATATGTTTATTGGCCTTTTATTATTTTAT
CTTTTGTGAAGTAGCTGTTCAGATCTTTGTCTATTTTTCAATGTGGTTGTTTGCCTTTTTCTCACAGATT
CTTTCATGGAAATACTTCATATTTAAGATAATTATCTTTTTATGGTTAAATGTGCTAAACTATCATCTCT
TAGTTTCTGTTTGTATTTTTATAATTTTTATGATATATTTTTAAAGTAATTTAAATACATGTATTTTAAT
GTTGATTTTTTCAATTGTTTCCTCTTATTGTTTTGTCACAAATATATGACAAAAATCCTTCACTTCACTA
AGGTTATAAATTATTTTGCCATACTTTCTGGTAGAACTTTAATTTTTTCAACAGTTAACTTATTAGCCCA
TTTATACCTAGTGTCCCATTATCGGAATGCTAAGCTTGTGGGCATTATTGATATCCAACTGCTCAAGGTC
ATCATCAAGGTCTGATTCTTCACAAAAAAACTTTTGCAGCTTCCGGCATAAATGGGTTGTCAGCAATTCT
TTGGTTTTCATCTTTTACATAAGAAAAATCAGTTTTCCCAGCACACTACACTGGGCGATCATTTCCCTGC
GGATCTCTAATGCCAGTTCTTTATCATCTCACATTTCCACATATGAAGAGAACTATGCTTCTGAGCTCAG
CTCTCTATTCTGTGCCATTGATCTGTTTGTCTATCCCTGTGTACACACCATGCTACATCACTAGAGTTTT
ATAATAAGTTTTAATGTCTGCTAAAGCAAATCTTCTCAACTTGATCTTTTTCTTTAGAAGTGTCTTGGTT
ATTTTGGCCCTTTGCTTATTTATGTAAATTTTTAAATACATTTTTCAAGTTCCACAGAACACATTGCTAG
GATTTGGACTAGAATTACATTGCATCAATAAGACAAGTGAGGGAGAACTGACAACTTTTCAACTCAAGGT
CTTTCTATGAATGACATGAAATAGCTCCATTTATTTTGGTCATCTTTAATGACATTCTATAGCATTTGAT
AATTTTCAACATAACAATCTTGCTTATTTTTTGTTAATTATCATTCCTAAGAATCTTAAGGTTTTTGAGC
TAGTGCAAATTTAATGACATTCTCTAACTATTGCTATTTAGATGCATAAAAATGCAAATTGCTCTTGTAT
AATAATGATAGTTACTAACTGTATGCTGCGTTCTACTGTACCAGGTCCTGAGCTAACCTCTTTATATACT
GATTAAATCCTCTCGACAACTCTATGAGCTAGGTCCTGTTATTATAACCACGTCTCAGATTAGGAGACTG
AAGCACTGAGAGGGTTCGTTAATTCACCCTTCTACGAGCTCTAGCAAGTGCAAGACTGGAGTTTGAACCC
CAGAATCTGACCAGTGTTTAGGCTCTAGTGTATGGCCTATCGTGATTTGCATCTGCTATGCTCAAATTGT
TTTTGAATTATATTTGAATAACTTAAATTTTAAATAATTATATTTGAATAATAGAGAATTTAATAATTCT

FIGURE 3 (continued)

CTATTATTTGTGATGCAGTCCTATAATCATATAATCTAGGAATACGGTTTTGTTTTGTTATTCAAATTAT
TATGCTTTTGTATATTGTTCTGGCCAAAACCTAGGGTTCACTACTGAATAAGAGTAATGGGCCAGGCATG
GTGGCTCACATCTGCAATCCTAGCACTTTGGGAGGCCAAGGCAGACAGATCACCTGAGCTCAGGAGTTCG
AGACCAGCCTGGCCAACATAGTAAAACCCTGTCTCTAGTAAAAATTAAAAAAAAAAAAAATTAGCCCGCGT
GGTGGCAGGGGCCTGTAATCCCAGCTACTCAAGAGGTTGAGGCAGGAGAATCACTTGAACCTGGGAGGTG
GAAGTTGCAGTGAGCCGAGATCATGCCATTGCACTCCAGCCTGAGTGACAGAGCGAGACTCTGTGTCAAA
AAAATAAAAAGGTACTGGAAATCCCCTCTCTCCTTTGTTTATTAAGAATTTTTCTCCTGAATACGTGTTA
AAGCTTAATGAATGTTTTTTCCACACCTCTTGAAGTAATTGAGCAATTCTTTCATTTTGTTTAACCTGTC
AACTTGGTAAAGCATAAAAATTCATTTTTAAATGTTGCACCAACCTTACATTTTATGATACAAAATACTT
TTCATATAATAGTCTTATAATAACTTTGGGTTTGATTTGTCATAATTAATTAATTAATTAAAAATTAAGT
AACAAAATATTAAGAACATACCTATTATCCAACAGTTTAGACTGGCTTTTGATGTTCTGTTCTTGTACAG
TTCATATCTGATTTTGGTATTGATATGGGTTGGGTCTGTGTTCCCGCCCAAATCTCATGTCAACTTGTAA
TCCCCAGTGTTGGAGGTGGGGCCTGGTGGGAGGTGATTGGATCACAAGGACAGATTTCCTTCTTGGTGCT
GTTCTCATGAGAGTGAGTGACTTACCATGAGATCTGATTGTATAAAAGGGCATAGCACCTCTCCCTTTCT
CTCTTCCTCCTGCTCCAACCATGTAAGACATGCCTGCTTCCTCTTCACCTTTCGCCATGATTTTAAGTTT
CTGGAAGCCTCCCCAGAAGCAGAATCCTGTACAACCTGTAGAACCATGAGCCAATTAAGCCTCTTTTCTT
TATAAATTGCCAGTCTCAGGTATTTATAATACCAGTGAGAGAACGGACTAATACAGGTATCAAAGTTATA
TTAGCTTTATAAAATTAGTTGAAGAGTACGCTTTTATTTTTAAAATAATGGCAAGATATTCTTTTTGTAA
ATGTAGATCATCTCTTTCTTTTCGTTTGCTGAAATTTACTTGTAAAATCATCTGAAACTGGTGTTTTCTC
TATGGGAGAACGTTAAATTTTTGATTTAATTTTTTAAATGTTTATAGGCTCATTCAGGTTGTTTTTTTCC
TTACAAATTTGGTTTTGTAAATTATACATCTTCTTGAAGACTTTTCTGTTTCTCTTAGGTTTTCAAATAT
ATTGACATAAAGTTGTTTATGGTATTATTTTATTATATTGTAATCTCTGCTGCATCTATAATTATGTCTC
CTTTTTCATTTTTACTCTTTTTTATCTGTGCCATCTTGTATTTTTTTCATTGCAGTTAATCTTTCTGGAG
GTTATTTTACTTTTTCAAAGAATCAAGTTTTCATTTTTTAGATCCTCTCTATTATATTGTTTGTCTGCTG
TTTCATAAGTATCTTCTTTTATTTTTAGTATTTTCTTTCCTCTGAGTCATTTGGGTTTATTCTACTTACA
CATTTCTAATTAAGTTGGATGCATAGGTTTTTTTCAGCCTTGTTTTTTTCTAATACAGACATCAAAATCTA
CAAATTCCCATGAAGTTCCATTTTAGCTGTACCCCAAAAGTTTTTATTTTACTTTATTTTGTCATTGAAT
TAGAACTTATACAAAGTACTCTAGTCATAAGTATATACCTAGTGATTTTCAAAATAATAGCTAATAATTT
TAATCCATGTAACTATCACCAGATCAAGACATAGAGTATTTCCAGACTCCTAGTCAATTACCCCACGCTA
CTTCCATCGTCTCTGACTGCCATAATACAATACCACAGACTGGGTGGCTTAAATAAGAGAAATTTGGTTT
GCATTCTTGAGGCTGGCAGTTTGCAATTAGGGTGCCAGCATGTCTGGGTTCTAGAGAGGACCCTCTTCCT
GGGTTGTGGACAGCTGCCATCTCTGTGTCCTCATGTGGCATTTCCTCGGTGTGTTAGTCTCTCTTCTTTT
AAGGGCATTAATCCCACATGAGGGTTCCCATTCTCAAGACCTCATATAACTCAAATTACCTCCCAAAGGC
CCCATCTCTGAAAAACATCAAATTGGGGGTTAGAGCTTCAACATATGAATTTGAAACAAAAACATTCAAT
CCATAACACTTGGCCACAGAATATACCTATGTACTAAGGCAGCCTTAACTTTCCCTCAGCTTGACTATCT
TTAAATAGGTTTCTTCTTGCCTCTAGGTGCCTGATCTCCCTCTCATCCCAGCACTCACGGAATCCAGATG
ACATAACCACATGGCCATTTTATCAGAGCACTGACTTTAGAAAACTTGTCATTGTCGATGATTTCTCTGT
TCCTTGGACATGTAAATCTTTTTAAAAGCCTCTTGACAATTTTTCAATGCAGGACTCTTTCCTAAGGACC
TGGGAGCTGTTTCAAAAATCATCAAGGAAGATAGCATCTTATTTCCCTGTTTCTGTGGGAGGGTGGGAGA
ATAATATCAGCGGGCACCTTGCTTGAAGTTGTAAAATTACCTCCTGCCATGAAGATATGAGAAAATTTAT
TTTTCCTTTAGGTAAGGCCAAGTAGAAAACCCACATGTCCTAATACCTCTCCCCACCCCAGTTCTCAAAA
ACTCTCCAGCCCTTTGTTTTAGTGAAGTTGAGCACAGACTGAGATCTGATCTCTCTCCCCTATAGTAATA
GCATTGAATAAACACTTCCTTACAGGCTATCTTAGTCTGTTCAGGCTGCTAAACAAAAGACCATAAATTT
GGTGGCTTATAAACAACATAAATTTATTTCGTACAATTTTAGAGGCTGGGAAGTCCAAAATCAAAGTACC
ATTATATTTGATGTCTGGTAAGGGCTTATTCTCTGCTTTATAGATGGCACCTTCTCACTGTGTACTCACA
TGGCAGAGGGGCAAGGTAGTTCTCTGGGGCCCCTTTTATGAGGACATCAATCCCATTTATGAGGGCTTTT
TCCTCAGGACCTAATCACCTCCCAAAGGTCCCACCTCTTAATACTGATACATTGGATGTTGGGTTTCAAC
ATATAAATTTTGGTGGAAGACGGCATTCAGGTTATAGGACATGCTTAACTTTGCTTAGTGCAACGTTTGC
TTCAACACTATTAGGCTTTTGTAGATATGGCCAATTTTTTGAGTGTCTTTACTAATTTATTCCCAAGAAA
AATGTAGGAGAATTCCAGTTGTTCTACATCGTTGCCCACTCTTGATGTTGTCAGTGGTTTTAATTTTACC
TACTTTGGTAGAGTTGTGGTGGTATTTCACTGTGCATTTCATATGAATGTCTTGATAACTACCATAACCA
AATCCTTTTATATTTCCTTCTTGGACATTTGAATGTCTTCTTTTGTATTTATTCAGGTGTTTTGTGGGAC
CCAAAGAAGCTCGCAGGTTGCAATTAGTTATCACACATCCTCCTGTGGCACTTCCACAGTGCTTGTCTTT

FIGURE 3 (continued)

TATGACATTGCCTCTTTTAGAGAGTTTCAGCCAATTATTTGGTAGAATATCCCTCAATTCAATGCCGTCT
GATGTTTCTGTACTTACACTCAGGTGCTGATAATGTTGGCAAGAATGTCACAGAAGAAGCTTGTGCTTCT
CAGTGTATCCTGTTAGGAGGCACAAGATGAGAGTTTGTTACATTCTTGGAGATAATGACACTAAACAACA
GAAGCATTCCTTTAAAGTTTCTGTAGAGAAAAATGTTCAGTGTGGCACCATTGCTAGATAAAATGAATGT
AAATAAATAAGTGAAGTAAAAATAAATAAAAATCAGCAAGCTTTCAAATTTCCAAATATTCTGAAATATT
AAAATATACTTTTTATTTAAAATAATATACATAGCTCTTAAAAGTGATCTTATCATAATCTTTTAAATGT
TAAAATATCACAGTTTATAAATAGGTATATGCCAAACCATGAATAACCACAGATTAGTAAGTGAATTTTA
GAAGTAGCCAATTTGGAAATAATTCAAAATATAGTTATTGTAATTATTTAATTGCCATAAATTTCTCAAG
TTCTCTAGGGCTTTTTTCCTCTTCTCTATACCGCTTTTATTTTATATCAATTCAACTTACTGAGAGGAAT
TTTCAAGGCTTTTTTTCTTTTCAGCAAGCCTGTTAGCCATGCTAAGCAAATACTGAGTGCCAGGTTTTTT
AACTTAATGACAAGTGGCTGGAAACTCTGGTGAATGTCTTCCTCTATATTTAAGAAAATTTATCTGTTGA
GAAAAACACTTTAAAATTACCACTATTGTCTTCCGGTCTCCAAAAAAGATATAGGCAAAACAGTTTTCTC
AAATACTCCATAAAATTTTTCCTTTAAAAAGAGATTATTTTATTTTAAACAAGAAATCAATACCCACTAG
GAAAGCAATACCATGTCAGAGTGAGAAAGAGAGTGTGTATATCCTCCAGAGGCCAAATAGAATGTAATTT
TAAAATGTGCAATGGTTAATTCTGTTTATCAATTTTTCTGGGCCACAGGATGCCCAGACATTTGGAACAT
CATTATGCTAGGTATGTCTGTGAGGGTGTTTCTGGGTGAGACTGACATTTTGCAATGGTACACCAAGTAA
AGCTGACTGCCCTCCTTAATGTGGGTGGCCCCCCTCCAGTCAACCAAAGGCCTGCATACAACAAAATGTC
TGAGTAAGAGGAAATTTCACCTGCCTGACACTGGAATTGGAGCATCAGTCTCCTCCTGCCCTCTGACTGG
AACTTACACCACCAGCTCTCCAGGTTCTCAGGCCTTCACATTCAGGCTGGAACTACTCCACCAGCTTTCT
TGAATCTCCAGCTTGCTTACTGCAGATCTTAGCACTTCTCAGTTTCCGTAATTGCATGAGCCAATTTCTC
ATAACAAATACACACACACACACACACACACACACACACACACACACACACATTTGTCCCTCAATATCCAATGG
AGTTTGGTTCTAGGACCTCCCACAGATACTAATACCCCCCGGTGCTCAAGTCTCTGATATAAAATGCCAT
GGAATTTGCACATAATCTATGCCTTTACTTCAACATCACTGCCTCAGCGGCTTCCCCAGTCCCTACCCTG
GAGATGGTCCCCACTTCACTCTTTCCCACCTGCACTTCCTCAGACTAACCCATCAATCACTGCATTGTCA
TTACTCCTGTGATTGGCAGCTCCTCTACCAGGCAAACTCTCTAAAATCAGTCCCGGTGGCCCCAACTCAG
CATCAGGAACAGTGCTGGGTAAAAGGGGGCTCGACAACGTGGAACTGAATAAAAGAATTAGGAGGGACAA
GAAGTGCTTGCACTTAGAAGTGGATTTGGAGCGCTAGTTTTAGCAGGACCTTTCCTGAGAAGACTGAGGC
CAGGTGTCAGTAGGCAGGTGCCTGAGAAGAGAATGCGAGGAGAGGAGATGGAAATGCGGTCAGACGGCCA
AGAACGCAGGACTCCCGGGCACTGGTGGCTGAGCGTGCCGGGGGCTTCCATTCGGGCCTGCAGACACCCA
CAGACCTTATTATCCCGGCCCCGCCGGCTTGGGGGCCTTCTGCCTTCCTTCTCAAAGGGCACGACCGCAG
GCGGCGGCGACCACAGACGGCGGCGACTGCAGGCGGCGGTGGGGCACGAGTCGGCACCGAGGGCGGACCC
GCGGTCGGGGTGAGTCCCTACCTCCTGGGAGAGGCTGGGGCCGCGTGGGGGACCCGGGGCGGGGTCGGCC
GACGCCCCTTCCCCAGCACCCGCCCTCCCCGGCTTCTCCAAGGCCTCACCCCGCCGCGGGAAGAGCAGGT
GACCGCACGCGAGGGCCCCGCGGGGGACCCAGGGCTGGCTTGAGCGCACTGGCCTCCTGCTCTTGCAAGG
AGGACTCCAAAACGATTCTGAAAGGGAAAGTGTCTTGAAATTAACTGGAGGCCGAAACCCAGGGGAAGCT
GGTGGTGCAAAGGACTCATCCACGCTTTGGGCTGTTACATAGAGAGGATTTTGGAGGAGGGGCAAGAGAA
GTTGGGACCCTGGGCTTTTCTGTTTCAAGCAAGCAAAGGGAGGGTGGCGGACTCCTATTTCAGAGTAGGG
AGGAGCCTTGGGTCTTTATTTCTTACATGTATCAGGGACTCACCTGAAAAGAAAATGATGTGTGCCACAA
GTAATTAGTAGCATTCCTGACCCCATATACAGAGCCAGGCGTCCTAACTCCTGACACCTAAGCTCTTTTC
CACCCCTGGCGCTGGAGCCACGGTGCTAAGTGTGAGTGGTTCTGTCCCTGGGCTGCACATGACAGAAACA
CGTGCAGACTGCGTGGCTCAGACACAGAGTGGCTGGGGACACTGCTACGTCCTCTATCGGGGGGTTCAGA
GGCAGGGCGGGCTTCAGGCTGACTCAGCAGCCCGTGATGTCATCAGAGACTCACATTCTCCCTCACTCAC
TGCCCCAACTTCATCCTCAGGTTGGTCACAAGGGGCCTCCGCAACTGGAAGCATTTCACGTCCAGGACAA
GATGTCCAGAGGAAGAGAACAGAACAAATGACTTACTGAAGTAGAAAGCGTTTCCCAGACCTGTCCCCCA
GTAGATGCCCTTCAAAGTAGCCAGAATCCGTGCATTCTAACTTGAGCCTGGATTAGGGTGGGGCAAGCAG
GTGTCTAGGGTACAAAAGTTGAGAAAGCACGGGTCGGGCGCGGTGGCTCACGCCTGTAACCCCAGCACTT
TCGGAGGCTGAGGCAGGCGGATCACCTGAGGTCAGGGGTTCGAGACCAGCCTGGACAACGTGATTAAACC
CTGTCTCTACTAAAAATACAAAAATTAGCGACTGTGGTGGGCGCCTATAATCGCAGCTACTTGGGAGGCT
GAGGCATGAGAATTGCTTGAACCCAGGAGGCGGAGGTTGCAGTGAGCAGAGATTGCTCCATTGCACTCCA
GCCTGGGCAACAAGAGCAGAACTCTGTCTCTAAGTAAATAAATAAATAAATAAATAAATAAACAAACAAA
CAAACAGAAAAGAAAAGAAAGCAGAATCCTTAAATCGAGTGCCTCCTTACAGTAGTGCCTTAGGTCCCCA
CTCTGATTTTTTAAATGATGGTTTCATTGAGATATAATTCACATACTAAAAAGCACCCTTTTAATACGTG
CAATGCAGTGATTTTTAGTATATTCACAGACTCGTGACACTATCACCACTAATTCTAGGACATTATAAAA

FIGURE 3 (continued)

AAATTCACTTCCTTAGTACTCATTCTTGATTCCGTTAAAAAACAGAGATTGTCAGACTGGTTAAAAGTAA
GACCCAAACATATACTGTCTACAAGAAATTCACCTTGCATTTACACAAATAGGTTAAAAGTAAATGAAGG
TAAAATGTGCAACATACTATTCTAATCAAAAGAAAGCTGGGGTGACTATAATAACATCTAACAAAGTATA
TCTCAGAGTGGAGAATATTACTGGAGATGAAGAAGGTTATTTCATCATGATAAAGGAGGTCAAATCCTAC
ATAGCAATCCTACATTTTTATTCCTCTGCTAGTAAGAGAGATTCGAAATACATGAAGTAAAACCAAATGT
AACCATGAAGATAAAAAGTCCACAATTGTTAGAGAGAGCTGCCAGGTGTTGAGGTGGTCCATTAAGACAC
TGAGCCAAATGGGAGAGTGACAGTCAGGCTTTTATTCATTTGTGGGGGCAGGGGAGAGAGGGAGATTGGA
GCTGGAGTCTGGAGGAAGGGGAAGAGCTAGTAATGGAAAAGCACCGAGTATTGAGTCAGAGTGGAGAAAA
GTATCTCCAGGCCCCCTAATAAGGAGGTCTTGGCAGTGTCCCAACAGAGCCCCTGCCCCATAAGGAGGCC
TCTGAATGGAGGGGCCAGAGCTAGAAATGCAGGTAGGCACAGGGCATGGCTGGCCCAGGGGGTCCTAAGC
CTTTGATGGTGCCTCCCTCCCGAGATCACAAAGCACTAGCTATGAAGTCTGGTGGGAGAAGGGCAGATTT
CACCCAAGAGTAGAATATCTGTAATTGCATATGGTTGGGCCTGAAAGATTCCATTTAGGATTTTGTCCTG
AAGTTGTACTCTTCAACTTCACCTCTTAATTTTTCAGGATCCTTGAAAGAAGCAAAGACTACCCTATCAT
GGTCCTAAATAAATGGAATTTGCGGGATTATGACAATAACCCGGTAATTAGTCTGAGCCAGCAATGGACC
AAGTTCATCATTGAAATGTTTCCAAATAGGATGATAAGGACTTCTTGGAAGATTAAACATAGCCATGAGC
CCCCAACAATGCCAATCCAGGATAAGATGTTTCAAAGGTCAGCAGAGTCTGCTTTAGAGAGCCGGACTCT
TCCACTTTGTCAGATTCATTGATCCAGGTGCACCACGAGGTGTTGACAGTGGCACAGACTCTCCTTGGCT
GGCCAGCTGGAAGTCCAGGGCTATGCAGCTGCTCAAATACTCAAACCAAAGAGCTGAGGCTGATCTGTTG
TGTCTCCAAAACTAAGGTAGTGTTGTTAATGACCTCAGTGATGGTAAGAGACAGGTGCACAACCTTTTCT
CACTGAGGGACCTGAGCAGTGGGAAAAACCACCCAGAGCATACACATGAGCAAAGAGGGTCAGCAGTGCT
TCTCACCCGGTAAGCCCTCCAAGTAACCAGGGTAGGCTTGGTTCTGGAGCTCATGCCTTACTCAGCCTGG
TGCAACATGCTCCTTGGGAGAGGTTGCTTGGAATATTTGAAAAACTCTTATTAATGCCCCATTCGTGCAG
ATTACAAGGCTATCAAAAAGGAAGGTAAAGGCCTGGTGTTTAGAAAAGAAAGAATACTCTAAAGGTATAC
ATCGGGTTGGGAGTGTAAGAGTCATTGACTACCATAAGGTTCAACCCCCTAGAAGTCCTTCTTGGTAGGC
AGTAGGCAGAGTCCCTGAGTGGAACTGAAGAGTCTGTACAAGGAGGGGACAAGTGGAGGAGAGGAGAAGG
TCACCACCATCAAGGCCAAAATAGCCCAGTAACAGACCCAGGCTCCTCTTCCCAGTTGCTCCCATGTGGA
ACAGCATTGAGTTGACAACTAGGAAGTCATTTCGTTCCTACAGTACCAGGGTCCACATATCAGGTAACAC
ATTGGGTCCGGGTGTGTTAGGGCACCTGAGATGCCAGAAAGCTCCATAGTTGAAGAAATGTCCACTCATG
CTATTCAGTGGCATGGCAGCCAAAGATTTACATATGGGGTCAAGGAGTGAGTGGCATATCCAACTACTAG
TCAAGTTCAGCATGATGGCAGCTGCCTGAGTCAGGCCTACGAATGAATTTTGTAAGGCCAGAGTCACACA
GACTACCCATGAGAGAGAGGAGAGAGGTTAGATCCCACTTCTTGCCCCGTATCTGAGTTCACAGGACCAA
AGGTTCTCATGTCTTATTAGTTCAGGAGACTCCTCATTGACTGTGACATGGGCAGTCTGTCCCGTGCCAT
GAGCAAGAATAGTGCTCTTAATTCATTCTTAGAATGGTGAACCTAAATATTCTGGCTTGGCTTCTCCTGG
GGTTCCATCAAAGTTTCTATTTGATATTTGATATGTATCCCATGGGGCTACACGGAGTAAAGCAGCAGGG
CCACCTTAGGGAAAATGTTGAGACATTGAATTGATGGTTATTATCTTTGAAGTCCTTGTAGGCAAAATTC
AGGCACTGCAACCAGGGAGTAAATGGAGAAGCAAGTTCATGCCTCCCAATCTGTGCTGTTTAGTAGCCTT
CCTGATCTCCCACTGATTTTGGTCTTCAGGAAGGGCTCAAAAAGGATGGAGGGAACTTGCATGATCCACC
ATGGAAACTGATTTGCCAATAATTTTAAAAGAGGGGTGTGCAACTGAGGGAAAGAGACAGATAGCCCAAT
CAATCACACAGCACAAATGAGAAGTGCACTTAGAGAATTGCCGCAGTGAGACCCCAAATTGCACACCTGA
GACATGTAGCCAGGCTGGGATTATATTGTCCATTTCCATCAGCCACTTCAACCTGTTCTTTTCCTGTTAA
AATATGCGATCATTGCTGTGGCTTGTAGATGATACAGAGCATGGAGAATCCATCATGCCTCATAATTTGA
CCCATGTATAGTTTGGGCTGCAAATGTATCGTTTGGGCCATTATTAGATACAATGTATTCAGGAAGCCAG
AGAAATAAACAAATATGGTTTTGGAGGGACTGAAGAGTGTTGCCTGAGTCAGGGAAACACATGGGGATGA
CTAGTCCAAATACAGAGAACTCATCAACTACATTTAGGATCCAGCAGAATGCTCTGGATGGGATGAGGGG
ACTAGTGTGATCAACCTGCAAAGAACATCCTGGCCTTTTTGACCAGAAGGATCTGTCCCTGAGCAGAATG
TTTAGCCTTGCTCAGGGTCTGGCGGGTGGATTATCTTTTTCATGCTGTGTTGGCATCTTTTGAAGATAAT
AGTTCATGCATACAGATCCAGGCTAGGATGGCATCTTGATTCCCAGGGCCCTTCCTCTCATGGATCAGAG
GCAATGAGTTGAATATCTGTTATCTCTGGGGCAGATGACAAATCATTCTCCATGTTTAGCTGACATGCAC
GGTCTGCTCATTGCCTTGATTGGCTCATTGCCTTTGTCAGCATAGGGAGCTCTCTGGTGAGCACCCACAA
GGATAACAAAGAGCTTATTAGGAGTAGAATTGAATTTTATCCGAATGTCTCATCCCAAGAGAGGGATGTG
TTTTACATGTCAGCACAATTTTGCCAGTAGCTCAATCAAATGTTCAGACCATTAACTACAGCCCATGAGT
CAGTGAAAATATAGCAGGGCTCCTTTGTTGAGGGAGCCTGGGTAGCCAACCATACTTTATAAAGCTTTGC
ACATTTATGCTGAACTTGCCAAGGGATAGATCTATCTCAGGTTGTATGACAGCTGCACCTCATTCCAGCA

FIGURE 3 (continued)

TAGTAAATGTTAATCAAGAGACACCGTCAGTGAACCAGGCTTATGTGTGGCCCAGAAGGTCCTTGTATCT
GAGTTCCCATTGGCCAAGTGAAGGCAGTGGCTCATTGGACGACATGCCTGGGAGGGGGACAACACTCCTG
AGTCCTTGCCATTGAGTTGAAGGCCCCAGCTGGGCTGGGTTTTACCTGCTTCTGTGTAGAACATTTTCAT
TCACTAGAGAATACTCTTAAGCCACACCCACCTGGATATTTGAGGCCTCTGCTCACTCATAACATGATTG
GAATTTGGGATCATAAAACTATGTCACAGCCGTGAGTCACGTACTCATGCATATCTACCTAGGCCCAATA
ACAGGACAATAATTGTTTCTCAAAGTGTATGTGCCTTTTGGCTGACTCCCTTTCAGCTGACTCCAGGATC
TTATAAGTTGAAAAACCCAACAAGTGTCTGATGTTATTTTTCTACTATGAGCGATAGTAAAGGAACTGAA
ATGTTGTTGAGACCTGTAAGTCGAATGGCAAATGTGGATCCATGGGGTCCAGGGGAAGGGAGGGTACTTG
GATGGCTGTGGTAGCCTGTTGAATGGGCCCCATTGAAACATAGCAGCCTTTTCTAGTAACCTCTTAGTTG
GGTCCCATCAAAATCCCCACAAGGGAAATGTGACAGTAACAGTAGATGAATAAGCCCACAAATCACTGGG
CATCCTTTTTATTTGCTGGGGCAGAGACAGCCAAAAGCTTGGCAGTCATCTCCTCTAAACGAGATGTTGT
GCCACTTGCCCAGATTACAACCAGGAAATTCACTTGGGGTCTCTGTCTGTTAATGGTGTAGTTGGGTTGC
TGCGTGAAAGTCATCAGTCCTCAAGCACCTAGTCCTTATTTGGCAATGTCTTTGTTTGGGTTCACAAGGA
GGATGTCATCAATAGAGTGCAAGGCTAGTGCTTCCTCCAGGCAAGCAACTCTCCCCAGAGCATAACCTAT
TCATTGATGGCAGCTATGTGGGGAATTTAGGTCACTTTGTGAAAGGACATTAAAGGTGGATTGCAACCCA
TTCCACATAAAGGCAAGTTGATCCTGGACTTCTCCGTGTGGGAGGATGCTGAAAAAGGCATTGATGATAT
CAACTGTCCCATACCAAGTTCCCTCCAGTAGCCTCTGTAAGAATCAAAATGTCAGATACTGCCAATGCAA
AGAATGGCACCACAGGCTTGAGCCACCTGTAATAGACAGAGGATCACCAGGTACCTGAGGCCATGTGCGC
AGGCCAGACAGAGCTACTGTATGGAGGAACAGTTTCTCAGGAACTTTGCCTCAAGCTTAGCAATTGAAAC
CAGCCCAATTGTCCCATAAAACTAATATTTATGGTTTATTTTGAAAAAGCATATAAATTAACCCTCATAG
TCTTAAAACTCAAGAAAATTACAGTTATCTGAGTTCCTTTCTCAGGAAGCCAACCATCAGTGCTTGCAGA
TATTATCAAGCAGCTAAAACCCACCAGGTCTACACATCTGGACAATGAGAAACCCGACCCCTCACCCATC
ATGATGGCCTACGCAACCACCTGCTTCCTGTTGACCAATTCCTCTTCCTTACTTCTCCCTAATTCCTGTT
TCCCCACACATGGTTACATTTCTTCCCTGCTATATAAATTCCTAATTTTAGCTGGTCAGGGAGATGGATT
TGAGACTTATCTCCCATCTCCTCAGCTGTAGCACCCAATTAAAGTTTTCATTCGTCTTTGCAATACTCAT
TGTCTCACTGATTGGCTTTCTGTGCAGTGAACAGAAGGACCTAGATGGAATTCCTGATGTTTTAGTGACA
TAATGACAGCAGTTATTTTTTTCCTCTCTAAAGCAGGTGGGGATACAATGGCCTAGGCGACAGTAATTGG
GTACACTCACAGCCTTTCCCATGTCCCACTAAGATGACCCTAAGTGCAGCAATTTCCATCAGGGATTGAG
GGTGAAGGCCAGTAGGGGCACATATAGACAATACATCTATACCAAGAACACATGCAGTCATGGGAGCCAT
AACGTAAAGGCCTCTAGGGGCCCAAAGGTCCCTTCCCAGAGACAGAGCAGGTGGTGGTGGTCTCAGACCC
TAAACCAGAGAACATTATCTGTTTCCCCCTCATCCTGGTGCCAGGGATTGTGGGGATCAGAGGTAGCAGT
GCACAGATGTTCAGCATGGCCAAGAAGGACATTTCCTCCCACCTCCTCACTGAACTCTGACATTGGCTAG
GGCTTCTAGTCATCCCTGGGGACAGAGGGACCTCAGCCTAACCCCTAGTCTTGTTAATTTGTAAAAGTCT
AGCTGTCTGGGGAGAGGATCGTGAGGCTCTTCAAGTCATCTCCAGAGTCACTGGGAGGGATGACAACAAG
CATAATGCTTGAATCAGTCATAGGGGCTATCACCATGCAAACCCTCGTGAGCTGCCTGCTGGGCCCCCCA
TGGTCTGGTATCTTGGTGAGGAACTCTTCAGTCTCCTCCTTTGAGAGCCCCTTTATTGAATCATCAGGCT
CAGAGAGCAATTTGGGAATGTCATTGCCTAGATCGTCCAGTAGAGGGCGCCGGATAGTCATCTTTGCCTC
CCTGCTTCTGCAATCTGTTTTCTTGGAAGCAGCCACTCTTTCCATGCCTTAGGCATTTGTTAAAATAGCT
GGATTGTGTCTGGGACGGACTGAGCTGGCCTTATGAGGTTTACCTGGGCTTGATAACCAGCAGTAGTGGC
ATAAAAATTCTTGAAATCTGAGTCTGGTGAACAGTCTTATCCTCTGCTTCCCCCAGCCCCTCATTGTAGA
CCCAGAGGACCCCCAGGGTGACTTGCGGGGCTACTATAGCCTCTGCGAAGGGCATCCAGAAGTGTTTTTC
AATGGCATGGGTCTTGTTACAGTGTACCAAACCTGCCAGATCTGTCGGAGCCCAAGTAGTACCCAGCTGA
GGACCAATGATCCCCCTCGGAACCGAAAAGCTTCTGTAAACAACACATTAGCACACTCTAAGGGTGCCCT
GCGGGGTCCACTGGCACCTCCCAGACACCCCGTGGCATGGCTGGCAAGTGTTCTGCGGTACCCTCAGACT
CTTGCAGATGAACCACCAGCACCTCTACTGTGCCCTGAAGGACTTTTAGGCTTTTTGTTTTTCCAAAAAG
GCATTGTGCTTAATTGACCACTCAGCTCCTTTGTCAAATTGAGAGAGAGAGAGAGAGAGAAAGAGAGAGG
GGGCATGTATGTGAGTACTTTCAGGTGTTAAGGTGTTGAATTAGGACAACTAGCCCCACTGAAAGTAACA
GTCAAGCTTTTATTTGCTTACTGTGATAAGAAGAGGCTACCCAGGACATGGTGCCATTATTTTCCCCATG
GAACAGCACCAGGAAGGGTCAGATGACAAGCAGCAGAGGTGGGAGAATTGTCTCATTGCCTAGAAGTCCC
AAACGCAAGGTTCCTGCCATTTTGTGGACCCAGGAGCCAAGGGGAGGGACAGGAGGGATGGGATGGGGGA
AGGATGGACTAGAAGTGGAAAAGTACTGAGTGCTGAGCTTGAGTGCAAGAGAGTGTCTTCAAGGCTCCTG
ATAAGAAAGTCTCTTCAGAGGCTCCTGAACAGTGTCTCAGCGAAGGCCTCTGCTCCCCTCATAAGGAGGG
CTCTGAGTGAAGCTGTCTGAGCTCGGAATGTAGAGATGCATAAAGGCATGGCCTGGCTCAAGGGCCTGAG

FIGURE 3 (continued)

TCCTTGACTGCAGCTCCCACTGGACACTTCAATGCCCTGGCTGTGCACCAAATCTGTGAGCAGGGCAGCT
TCCCCCCACCTCCCCCATGCAGCCTGCCTTGTAGTTGCCTATGGTCAGGCCTATGGGATCACATATGGGA
TTTTGACCTAGAGCTGGACCTGTCAACAATTATAGTTGGACATGTCAACACTCATCTCTCAACAATTGCT
AGAACAGGCAGACACAACATTGGTAATTATATAGAAGACCTGAACAACACTATCACCAACTTCATGGAAT
TCACATTTACAGAGCACTACACCCCAAAACAGCAGAATATACATTCTTTTCAAGTGATCATGGAGCATTT
CCTGAGATAGACCATATTTAGGGGCATAAAATAAATCTCAATATCTTAAAAGAATACAAGTCATTAAAAA
CATGTTATCTGACTATGGTGAGATTCAATTAGAAGTCAATAACATAAAATCTTTGGAAATCATCAAAACT
GGAAACTAAAAATTACACTTTCAAATAATTCATGAGTCAAAAAAGAAATCAAAAGGAAAATCAGAATGTA
TTTTGAACTGAATAAAAATGCAAAGGATATCAAAATTTATTGATGCCACTAAATCAATACTTAGGGAAAT
TTTTTATGGTGGTAAACACCTATATTAAAAACCAAGAAAAGTTTCAAGTCAATTACCTGTTTCACCTTAA
AAAAACTAAAAAAATACCCAAAATGTAGAGAGCCAGCAAAGGGATCATGACCAACTCAGCATTCCACTGG
AGGCTATATGATCAAACAGCAAACTGTTTATCATGAATGCAGGATGTGGGTAAACTCACACTGCACCTGC
CGCCAAGAGGTTTGCTGAGGGTCATCACTCCCTGGCACCAGGCTCCTTGAAGTTATCTACTGGAAAATCT
AGCGCCTATTGTTCAAAGGATGCAGTGTCACAAGCCTGCTGTGAACCAAACGGCCGACTGACAATTACCC
GACAATCACCCCCACTTTTTTTGCTATCTCTTTTACCTAATAAATACGGAGGACTGAAAAAGTTTAGGGC
CCTTGCCTACTAGAGGCAAGGTGCCCCCGACCCCTTCTTCCAAATATACTCTTTTGTCTTTGTCTTTTAT
TCCCGCGTTCATCCTACTTTGTTCAGTGCATCAGGGATCGTGGTCGGTTACATCAAAAAGTGAAAAAATT
AAATGTGAAGTAATCAGAAAAAGGAAATAATAAAGATCAGAGCAGAAATCAATGTTGTGGACAGAAAAAC
AATAGTGAAAATCAATGAAACCAAAAGCTGGTTCTGAGAAACAGCAATAAAATTTATCAACACCTAGTCA
TACTGATCAGAAAAGAGAAAAAGGCACAAGCTACTAATCTCAGAAATGAGAGCGATGGTATTACTACAGA
TTTTACAGCTATTAAAAGAAAAATAAGAGACTATTATAAACAACTTTACAACAGTAAATTTGATGACTAG
AAAATGAACAAATTCCTTGAAAGACACAAGCTACCAAAGCTAACTCAAGAAGAAATATGTAATTTGAATA
GTTCACTATCTATTAATGAAAATAGAGTTGCAATATAAAGCCACTCCAGTCTCGGATGGTTTCACCAAAC
ATTAAAGGAAGAAATAATACCAATTATACAACATCTGTTCCAGAAAATTGCAAAGGTAGGTATGTTTCTC
AACTCATTCTTTGAGACCAGAATTACCTAAAACCAAAGTGAGACAAAGATATTACAAAATAGGAATAGTA
CAGACTAATGTCTCTCATGAATGGAGATGAGCAATTCTAAAAATATTTTAACAAATTGCATCCAATACTA
GACAAAATAGGAAATACATCATGACCAAGTGGAGTTTCTCCCAGTAACGCAAGATTGTTTCAACATTCAA
AAATTAATCCCAATATTAACAAAACCATATGATCATCTAAAAGAAACAAAAAAGCATTTGACAGAATCCA
ACATCTATTCCTGATATAAACACAACAAACTACGAATAAAAGAGACCTTCTTCACCTGTTAAAGGGCACC
TATGAAAAGCCTACAGCTAATATCACGTTTAATGATGGGAGCCTTCGTGCTTTCCCCTAAGATCAGGAAC
CAGACAAGGATGTCTGTTTTCACTACTTCTAATCAAGTCAGTGCAATAAGGCAAAGAAAAAAAAAAAGCT
ATCTAAATGTGAAAGAAAGAGGAAATTTTGTCTTTATTAGCAGACATGGAACTAGAAACACAGCTACTAG
AACTAAGTGATTTTAGCAAGTTTGCAAGATATAAGGCTGAGATACAAAAAAAAACCTGTATTATATTTCC
ATATACTAGCAACAATTAATCAGAAATTGAAATTAAAAAGCAACACCACTTATAATAGCACAAAATAGAA
TATACTTAAGGATAAATCTGACAAAATTTGTGCCAGACTTGTATACTGAAAACTACAAAACTATGCTGAG
ATTAATCAATAAAAACCTAAAAGAATGAGAAACATGCCTTGTTCACGGGTTGGAAGACTCAATATTGCTA
GTATGTCTATTCTCTCCAAATTGATATTTAGAATTCACACAGTCCTAATCAAAATTGCAGCAGGCTTTGT
ACAAGTCAACAAGCAAATTATAAAATTCACAGGGAAAGATAGAGGACTGAAAGCAGATAAAACAACTTTG
AAAAATAAAGTTGGAAAACTTATGTCACTTAAGTGTTTTCAAAACTTATTATTAAGCTACAGTAATTCAG
ACAATGTGGAATTGACATCAAGATAGACAAGCAGATCAATGGAATCCAATAGAATCCAGAAATAGAACCA
CATATCCATGATCAACTGATTTTTGACAAAGATGCAAAGGCAATTCAGTGGAAAATGGATAGCATTTTCA
TCATATGCAAAACATGAACTCAAAATTGATCATAGGCCAAAAAGGAAAATTAAATCCGGTAACACTTCTG
GAAGAAACATAGGAGATCCTTGTGACTTTGGATTAGGCAAAGCATTCCTTCAATATGACAACAAAAGCAT
TAAGCATAAACAAAGAAACAAAATGATAAAATGGACTTCATCAAAATTAAGAACTGCTTTTTAAAGGCAC
TGTTATAGAAATGGTGGGAATTGAACAATGAGAACACATGGACACAGGAAGGGGAACATCACACCCGGGG
CCTGTTGTGGGGTGGGGGGGAGGGATGAGGGATAGCATTAGGAGATACACCTAAAGTTAAATGACGAGTT
AATGGGTGCAGCACACCAACATGGCACATGTATACATATGTAACAAACCTGCACATTGTGCACATGTACC
CTAAAACTTAAAGTATAGTAAAAAAATAAAGTGTGCAAAATAAAGATTGAAAAAAAAAAGAAATGAAAAT
TGAAGCCATGAGCTGGGAGAAAAATGTTTTCAGATCACATATATGATAAAAGATTTGGTAGCCATATCAC
GAGATTTCTCAAAATACAATAAGAAAACAAAAGGCCAGGTGCGGTGGCTCATACCTGTAATCCCAGAATT
TTGGGAGGCCAAGGAGGGCAGATGACCTGAGGTCAGGAGTTCAAAACCAGCCTGGCCAACATGGGGAAAC
CCTGTATCTACTAAAAATACAAAAATTAGCCGGCTGTGGTGGCACACGCCTGTAGTCCCAGCTACTCAGG
GGTCTGAGGCACGAGAATTGCTTGAACCCAGGAGGCGGAGGTTGCAGTGAGCCGAGATCGTGCCCCTGCC

FIGURE 3 (continued)

CTGCAGCCTGGCAACAGAGAAATACTCTGTCTCAAAAAGAAAAAAAAAAAAAAAAACACGAAAACAAAAT
AAAGCAAGAAGCAATAAAATATCGATGAGACATTTAAAAAGACATTTCATCAAAGAACATATATGGATAG
CAAATAAGCACATTTTGGTTTTTTTTTTTTTTTTTTTTTTTTTGAGACAGAGTCTCGCTCTGTCGCCC
AGGCTGGAGTGCAGTGGCGGGATCTCGGCTCACTGCAAGCTCCGCCTCCCGGGTTCACGCCATTCTCCTG
CCTCAGCCTCCCGAGTAGCTGGGACTACAGGCGCCCACCACTACGCCCAGCTAATTTTTTGTATTTTTAG
TAGAGACGGGGTTTCACCGTTTTAGCCGGGATGGTCTCGATCTCCTTACCTCGTGATCCGCCCGCCTCGG
CCTCCCAAAGTGCTGGGATTACAGGCGTGAGCCACCGCGCCCGGCCTAAGCACATTTTTTTAAATGCTGA
ACATAATTAGGCATTAGGGAAATGCAACCAAAAGCCGGTACACGCTGAAAGTAACAACACTGGTAGTACC
AAGTATTGGTGAGAAGAGAGAAAAACCAGAACTCTCCTAGGCTTTACTGGGAATGTTAAATGATACAACC
ACTTTCAAAGGCAATTTGGCAGATCCTTAAAAAGTTAAACTTACACCTTCCATATGACCCAGCCATTCTA
CTTCTATGTATCTATATACAAAAGAAATGAAGACATATGTCCATACAAAGATGTATATATATAAATATTC
ATAAAAACTTTATTTTCAATAGCAAAAATCTTGGTAACAACGTAAATGTTCATCAACAGGTAAATTTGTT
CATCAACAAATCATGGTATACCTATACAAAAAAATGTTACTTACCAATAAAAGGGATGAACTATTGATAC
ATACAATAACATAAATGAATCTCAAAATAATTGTACTGAGTGACAGGAGTCATACTACAAAGCATAGATG
ATGTATGGTTCCATGTATGTAAATTTCTTTAAAAATGCAAATTAATCTATAGTGACAGAAAGAAGATTGG
TAGTTGCCTGAGCAGATCAGTGGTTGGGATGGGACGGGGAGAGGGAGAAGGAAGAGTGAGAAATTACAAA
GATGCAAGAAGGAATTTGGGAGTATGATAGATAGGTTCATTATCTTGAATATAGCGATGGTTTGTTTCAT
GGAAAATGTGTCAGAACTTATTGTAGAGGTTAAATATGTGAAATGTATTCTGTGTCAATTAAAGTGTTCT
TCAAATTAGAGGTGGAAGTGAGAACAAAACTCACAGATGTATACCTTTCAGTCCTGTGGATTAATTTTGC
CCAAACCTGCTTTGGAAAACATGATCCCTAAATGAATGTGGCCTAACAGATATATCCTGGCTTGGTCAAA
TTTAAGTAAGAGCTGTAATATGAATGGTTCATGTAACTGTTAACTGTCAGTCAAAAACAGAGTCAGGATT
AACCACTGTTCAGTCCAACTCATTAAAGAAATAATAAAGCAGGCAGCAGTCAGTGGTGGTATAAACAGTG
ACATAAGTGAGAGTACAAACCAGTGTAACTTTCTAGGGACCAATTTGGAAGAAGTCTCAAAATGTGCTCA
ACTTTTATCTCAACAGTACTATTGTTAGGAATTTTAAAAAATATATTAAGGATGTGAGCAAATATTTAGT
ATATCCAAAACAGCATAATATATATTATTAGCAATCTATTATTTGTTAATAGAAATAATTTTAATTACTC
AAACTGTCTAAAATTAGATTCAATTATAGAAATCCAGCCACACAGTGGAATACTATGCACATCAAATTGA
TGACCTGGAAAGATCTTAAGGGAGGTTTTTCATAAGGGAAGAAATAAGCTACTGAAGGATATGATTAACT
TGTAGTAAAATGCTTATAAATTTCTATTTGCATACACATAATAGGGAAGGATGTATATCACTATTAACAG
CAGTGATTGCTGTGTGTTGGAATTGTGGGTGACTTCAATTTTTTTGGAGACTTTGCTGTAGTTTCCAAAT
TGCTGCCACAACGCAATTTTATTTTTAGGCAGAAAAAAATTAATGTATATGGAGGTTCTTTCTTAACTAA
GGGGTGTGCTTGAGCTGTGTCTGAGCACATATGATTAGTTAGAGGACTCAGTGGTGTGTTGCGTAAGTTC
CTTTGGTATTTTGTGTGTTTCAGAGGGAAAAGGAATGGAAAGAACAGCATAGCAAGCTTCAGATATTTGC
CTCCTAGCTCAGTCCTAAAGTGCATTGCTGAGTCCCTGAACTTGTATCTCAGGCTTATGGAAAGATGAGA
AGGAGCTGTCTTCATTACAAACTGTGTGAGACAGGGGGCATGCAGGGCTGTCTATGTGACAGTGACAGAA
GCAGATCACTATTTCAGCTGCACATGAGACACAGGGTGGCTGCAGCTTTACTCTATAGGGTTTGCCCTTG
GCTTTGTGTGCAGTGTCACCTGGGCACTAGTCCCCTGTTCAGCCTGGCAGTGGTGGTGGGCAGAGCCGGG
CGGATGGAAGAGGGCTGGCTCCTGAAGCCCTGAGATGCTCCATAAGATCCCCTGAAACAATGGGCACAGA
CTTAGGTGAAGGCAGAGGCAATGGCAGGCACCCCAAACACTCCAAAACCAGCATAGCCTTCCCAGGCCCA
AATTTCATGCATCTGCGGCCTCAGTTATTCTCAATGGCTCTGGAACTTTCAGCAAAGACTTTCACACACT
ATCCAGTGCACACGCTTTATTTTGGCATTCAAGCCACTGCACCAACTAGGTCACAGGGAATGTTAATTAA
GGCAAGATAGGTAGAAGGAAAGGAGGGTATGTACAGCAATTGCTCCTCTTTACGGAGAAGAGAACCTGCC
ACAGAACAAGATGCAGTTGGTTTTGTGGTGCCTGATGAAGAAAAGAAAAGGGTGGTCTGCACAGAATCTT
GGCTCCATTCTGCTGCACCGGGAATTCCTGACCACAGCAGTGGCTGCGGCAGCCTCTGTGCCTTCCTCAT
TGACCTCCACGAAGCACTTGTGGGCAACCTTGGACAGAGGCACATTCTTCTCAGTTGACATTCCAGAAAA
GTCTGCCTTGGCTTCGTCAAAAGCATCGATCATTCCTAATCTTCGAAGGAAAGGCTCCAAGTCATAACTC
TCCTCCAGCTTTAATCTGGGAAGGAAAACTTGAACCTTACTTTTTGTCAACTTTTCTGAATTTGTCCAGG
CTTTGAATTTCTCATATGTAAGTGCTTTTTCCACCTAGGATAAGAAAGACTCAAACCTTAAAATTTAGAT
GACAATAGCCTGATACCCACACACCCATTTATTACCCCTCCCCCAATGACATGCAATTAGATGGTGAGTT
CTGGTCCAAGAAAATCTACAGATATTTTCTTTTATAAACACACCAAGATTTTCTCCCAAATTTTCATCTT
TTCACAGTTTTATGGAGACAAGTGTAAAAGAGCTAGTAAACACCTGAGACAGGCAGAAATTTTTAATAAA
AACAATTTGTACCTAACTCCTTTCAAATGTTAAAAACATTTTTTAACAGTTTAGAAAATTCTAACCAATT
CATTACATTAATCTTCATGCAATACATACTACTGTGAGTGGGAGAGATTGTTTGACAAAAGACAAAGAGC
ATGGCTCAGAACTCTGCTTCTGAGTCTAATGAGGGGACTATTCAGGGTTAAATCAGAGGGCAACTCAGAG

FIGURE 3 (continued)

TAAAAGAGAGGGAATTGTGTTTCATCTGAAGATGAAGGGAGGCATGAGAAGGGAGCATGAGACGAGAAAT
GGGGAATGCAAGAAGACTTCATCAGCATCCTTGTTTGTCCTCTGCCTGTCCTGGAGTTAGCTTCAAATTC
TTCAAGATCCATCACTCTTTCTATTTATCAATAAGGTAGAAAGAAAAAAGGGAGAAAGGCCTTCCACTAG
CATCTCCCCTTCCCTTTAACAACTGGAGCCCAGGTGGGTACTCCTCTCCAACGAGCATTGTTTTGATTTT
GACTCTATTTCTAGACTCTCCTAATTTTCTCATAAGTGGCCACAACAGATGTCATCCCTGACTTAGGGCA
GTAGCTTTCTGATTCCAAAGGGAAGCCAGGAAAATCAAGCAGCCCACCCTCAACATCCTGTGCATTGGTG
TGCCAGAGCTGACCCCTATCAATTGTTAAACCCTCAGTAGACTAAAGTCGGCCATGGTGGGAGTATTTAC
CATGTCATGAGAATCAGCAAACTTTATAAATGAAGGCTTCTCCCACCTCCCAGAGCTGGTTTACAAGTGC
ACTATTAGTCTTGCACCTCCTACCTTGCAAGTTTACCACTTCCCTTCCTGGACTCTGTTCCTTTTCTGTC
ACAGTAAGACTTTTCTCTCCTCTTGTATAAGGTAAATTTCCCACCTGTACTTTAGACTTTTGCTATTCAT
AGTGTGGTTCCAAGCATCTGTATCACTTGGAATCTTGTTACAAATGCAACATCTCAGGCCACACTCCATT
GAATCAAAATCTGCACTTTAACAAGATCACTAGAATCATATATGTGCATTAGTGTTTGAGAATCACTGCC
AAGATTGATCCCTACCCTTCTTCCAGGACTTTTGTGCAATAATCATTGGGCTTTCAAATAGACCTTCCAT
GCAGAATAAAGAATAATATTCCAAATAATAATATATTTAGAACTCTCTCTTCTTAGCTTCATCAAAACTT
GTCCACTCATATATGTATACACTCAACAGAAATGCATGAACATGTTCATCAAAAGACACACAATGATGTT
CACCCAGCACTGCCTGTAATAACCCCAACTGGAAACTCCTCAAATGCCAATTGGTAGATGAACATAAAGA
AATGAGCTCAGCTGGACTCCACAGATACTCAGGCTCATTGCCTGGAGCTTACCACGGCGAGGTCCGTGTT
GTCATCGGGAAGCAGAATGACCATGCTCAGCTCCTCTTCCACATAGGGCAGCTCCAGGACCTGGGTGTGT
ACCTCATCCGCATACCCCATTTTAAACTTAGCTTCCTTAAACATCATCTGCACTGTCTTTTTTTCCTAAC
GGAAAAATTAAAGTTCGATTACTGAAAAGTGGGTATAATTTACTAAAAATAGGATATATCTAACTCACAG
AAACTCTAGGTGTGTATAATTACTGTTTCTGCACATTTATGCTGATAGATATAAAATCTTCATTAGTACA
TCTTAGTATTGAATAGAACAAGCTATTGTTCCAGCAGATCAAATATTACCAGGTGAGAAAAAAAAAACAG
TTTGGTAAATGGAGAAGGACACAAAAATTGACATTATCCTTGGAAGAAGCTGTGTTTGCTTTTTTGAGAA
CATTCACAGAGAAGCTTTCTCATGGAAGCTTCCAACTAAAAATTCTTTATCGAAGTTAAGATAAATATTC
AGGCCCTTGGGCTGAAGGATCTGGTTAGAAAAGATGTACGGTCCAAACTCTGGAAAGTTGCCTTGTTGTA
GAATTGGTTTTATGGCCTTGGCTTTCTTAGGAAGGGGACCTTGAAGAGATGTGTAAGGTCTGCTGTTTTT
AAAGCCTGCATCAAATATATTTTTAACTTTCATATCTTTGTGCAATATGAGAGTATCATATTTGATGGAT
GTCAAATCCCAAGCTAACAACTATTGATACCAGCCATTTTAATATTCAAAAGGGAAGGTAAAGTTAGGCT
TTACATCTGCTAACTTTTTTTTCTTGTGCTCAGGATTGTATAACTTTGACTTTTAAGGCAATAAATAGGC
ATAGTTGCCACTGATATTGCAAAAAGGTATCTAACTAAATACAGAGAGTAATAGCATCATGCAAACATAA
TTCCAAGGCTTAGAAGAAATTCTCCTCCAATCCAAATCATATGACCAGAGATGGAAGGTAGATTTGATCA
AAGATGGAAAAACAAAACTATCAATACCAAAATTATTTTTGTTTCTCTCTTCCTTCCGCCATTAAAGATA
CACAGGAGGCATTAAATTCATTCAGAAAAGAAGCCAGGCACAGTGGCTCCTGCCTGTAATTCCAGAACTT
TGGGAGGATAAGGCAGGTGTATCACTTGAGGCCAGGAGTTTGAGACCAACCTGGGCAATATGACAAAACC
TTATCTCTACAAAAAATACAAAAATTAGCCAGGCCTGGTGGTGTGCACCTGTAGTCACAGCTACTTGGGA
AGCTAAGGTTGGGGAATCATTTGAGCCTGGGAGGTCGAGGCTGCAGTGAGCTGAGATTACACCACTGCAC
TCCAGCCTGGGTGACAAAAAGAGACCCTGTCTCAAAGAAAATAAAATAATATAATATAATTCAGAAATAG
ATTAAAATCAAGATCATGTCAAATAAATTATTCATTTTTCCAAGAGAATATTTCCTGTAATATTACTTTA
AGAAAGTAGCAGTATATCTGAAAAATCTTTCCCTACCTCGTTGGTTTTAAAGAGCATTCCCCTTGTGTAC
TTTCTGTCAAATTGCTCATTCCACTTTCCCTTGAAATAAATGGCATTCACAAGGACCAGCTTTGTCAGGG
GATCGACTGTCCCAGCATCCAGTACCTCTGAAATCTTACCTATAAAGAATATGAGAGTTTATTGCAATTT
GTGGGGAAATAAGCATTCTTTTACAAAAATCCCTTTGACACATAAGGCAGAGGCTTGGTTGAGAGACAGG
CTGGAGTTCTGTCTTTCTGGGCCCCTGATGAATTAGGCGATGGTGTTTAGCAGTGTGGCATACACAGTGT
AACATTTGTGCTTAAGAAAAAAATCTTGAAGTAGGAAGGGCAACTATCATTTTGCCCTCAATTTATGGAT
GTAGAAATTCAGGACCAGAGCATTTGCCAGACTTTTGCTGAGTGCACACAGGTGACAAGTGGCTGAGTTG
AGAACATCACCCCAGAGTCTTGATTCTGACTATGGGGCAGTCAACCTTGGCACTATCATATCCAAGCCTC
ACCGCTATTGTCATTTTAAGCCAGATAATTCTTTGTTATGGGGGCTGTCTTGTGCATTGTAGGATGTTTA
GCCAGCAGCATTTCTTCCCATTTTGACAACCAAGATTGTCTTCAGCCATTATCCAATGGCACCTGGAGGG
CAAAGCTACCCCTGGTTGAGGATCATTGCTCTATGCATATATTCAAACCTCATCAGACAAGGAAAGCTTT
CCAAAGGATGAGAGAACACAGATCTGTCAATGGGAGAAGGCAGCCTCTCTGAAGGGGGTGAATGGGGCAA
AGGAATTAGGGGGGTAGAATAGAGGGGCCCAAATTGAGTTGTCCAATGAGAGGGTAACAAGGTCATCTCC
AAGGTCCCCTTCAGCTCTAATATTCTGGGGGAAATGTGGGTGGTCAGCCTAAGGGAAGGAAGGGCATAAG
CAGCCCTGGAAGAGCAGTGACAGGTATAGGGCAGTGGGGGGAAGGTGTGGAGAAACTTCTAGGTTCCTCA

FIGURE 3 (continued)

GGTGACAGTACTGTTGAACAACTGGAAAGACCACTAGGCAGATGATGTATGAAAACACAAAAGGCTCTTC
CCTTCCCATGGTAATTATTGTATTGGCTTTCAGTAGAATCAGGGGCATTACTTCTGCTGGACACACAGTG
GTTGCGACATAGGATGGAATGGATGCAATAATGAGTGCTAGGTTGGCCCTTGAAATAAGTGACTTAATTC
CTCCACCGTTTACAAGTATCGAAATTACTTGTTAGGTATTTAGGATGCTTTAAAGTATGACTCCCCCTTT
TTCCTACTGAAGTAAAGAACTGGCAGAAATATTTCTGGTGGGATGGAATGTGGTCTGGGCAGGGAACACT
GCAGGCTCCATGTCGCTGCACCTCCAGAATAGGGAACAAATTCAGAAAAGGCCACACTCTGAGAGCAAAT
GTAGCCATGGCCAAGTTAAAAAGGAAGGAGAAGGCTGCAGATCAAACTACTGAGCTGTCCCATTACCACG
CGGAGGAGATAACATGAGAGCATGAAATGTTGCCCTCTCTAAGCCGCAACTTAATTGAATGCCATTCTGT
CTCCGAGCATGGAAGGGCCTCTCAGATAGAAGATTAACAGAATTCCAAGGAGGAGCCATTTTCCAGGGAT
TTTCCAGCACGGTCCACAGGGGAGGAGGTCAGAGATTCAACATTAGTTTTAGAAATCAGTACTTCATGAT
CTGATAAGAAATGACAGAGTTGCATTGCTGGCCTGTAAACTCAGCAAACACATACAAACAGGCCTGTGGT
ATGCAGGTCACAGTGGCAACACCCTGGGAAGTCCCATCCCAGTCAATCTAAGCCTCGTTGTATAGTAATT
CCAAATCAACAGAAATGAAACTGTCTCACCTTCAGTCTTCTCTGCCACCCAGTCATTTATATGCTTCCTG
CACTCTTCAGTGTCTTCAGCAAAGGACAACTCCTCCAGCTCTGCCTGATAGAACTTCTGACAGTATTCTT
TAAAGTCCTGCAAACACAAAACACTGAGTTTAGTCTCATTTGGTAAAGGTTCCCACAAATGCAAAAGCAT
TTTGTTTTCTCTTACTGCATTTCTACAATAAGTGCTTGGACAGGTCACACTCCACTTCAAGGTGCATGCG
TGCAATTAACAAAAATGTATGGGCCACCTATTCTTGCCTGGTACTGGGCAAGGTGCTTGGCTTGAGGAGG
TCCACAGCCTGAGAAGAGGCAGCTGAGACACCCAGACACTTACAGGACATCATGAGCTGCCACTATCCAC
AAAACATCACAGGAGCATCCTTGTCAAACGCTCTCCACTGACTTTAATATTGCTTCCCTCACTAGGCAGT
CTAACACACTTTTACTCATTTTGCATCACCAGCACCAACTACAGTATTGTGGTTTTGGTTAAACGAGAGG
CTTTATAAGGGAACTAGATTGTTAAGAAATCGTGTTGAACTGCAAAGAAGGAAATAGCATTTTAGATCTG
GGTCATATGGTTGGTTGGAAGAATACAGAGCAAGGAAGGCCCCATGGGAATGGAGCGTGATAGGCCTGGA
TCATAGGGTGTGTGTGCAACTGGGTTCATACGTGTGCATGCGTGTGAACATCTGTGTGCATGAGTGCACA
TGTGTACATGTGAGTGCTTGGGCACCTGCATGTGTGTGGATTGCATGCATGTTTGTGTGTGTGTGTACAT
GTGTATGTGTGTTTGTGTGTATCAGGGAGGGGATTAAGGGAAACAGTGGCAGGGGAAGAGCCTTGAAATG
TAAGTTGGGGTCCAATCAGAAAAGTCCTGTACCCAACACATTAAAACCCAGATAACTTACCTCACAAAAA
CCTGGCTTTGGATATAATAGGCCTGGAAACTGGCTCCCAGCCTCTGTCCATTCCCTGTTCTCAAATATTT
TAATTTCAGCCAAAGAAAGAGGATATAGAGGGAAGGAGGAGCCAAGCCACCAGGAAAAGTAGAGGTTGGC
TCCCTGTGTCCCAAGTATTACAACAGTAGTAGATCAGGCTGATGTTCAAAAATGAAATGGATTCATCAGG
AGATTCCTGGGATCCAGAGTCACCTTCTGAGGTAGATAAACCCAGAGCAGGCAAATTCCGGGAACAGCAC
CCAGCAGCTACCAGGACAGGGATGTATTTGAGCCTTAGAGGAGTCCTCTCAGAACCTCCAGCCAATAGGA
TGGCCAAGCTTGCTGCAATCAGTTCACTAATTTTAAGACAACATCACCCTGCATATCAGGTGGCATGATT
TTTGAACCTCACTGATTGCATTATGCCAGGCTGGACTAGGGAACCTTGGAATTATATGCTGAAGTAAATA
GAAACTGCTTAGATTTAAAACCTCAATTTTATGAACAGATTTTCATTTTAGAAAGACGATTGTGTCAGTT
GTAGGTGCAATTCAGAAGAGGGCGGGCAAATTTAAGAGAATTTGAGAGGCTACCTCAGCAGGAGGCAGCC
GAATAACCACACTTGGGACTGGGGAGGAGCTCTGTACAGCGTGTTGAATGATGTGGTCACTCAGGGACAG
GGAATTAAGGGGGAGAAGCAGGGCTGCGTGCAGGAGAATTGACATATTGGGATTGATAACAGGGATGGGT
GTATCAGTAACAATTTACAAAGGACGTAATTCAGAAGTCATCATAAAATCTAAAATTGTAATTTCAGAAG
TGTAATTCCAAGCACGTTTTAAGTCAGTACAGTTATACTTTATTATCTGCTCTTCTGTAGTCTAACTTAC
TTTCAATTTCTTTGTCATCAATATGTGAATACTACTTACTGGAAGGAAATCACACGTCTTTTCTCCAAAG
AGTCTGTTGGCAGTTCTAAGCAAGTACTGAGTGCCAGTTCTGTTAACTTCACTGAGAAGTGACTGGAAAC
CTCGGTGAATATCTCCGTCTTTGTATAAACAAAGTGCCTGGGAACAGAAACCAACACTGACTTTTAACGC
TGCCATTATACTCTCCCAAAGAGCTTTCTCCAAACAAACCTCTGTACTAAAAAAACCACACAGGATCCTA
CTTTAAAAAGGTTTGGCCTAATTGTCTAGCACAGGGTTTCTCAACGTGGGCAATGCAGCATTGACATTTG
GGGCCAGGACACTTCCTTGTCTCATATAAGCATTGTAGGATTTTTGCAGCACTTCTGGCTTCCATCCACT
AGATGTCAGTAGCACCTCTCAGTTATGGGATCTAAAACTCCAGGTCTTCGCAAGGGTCCCCAGGAAGGAA
AAATTCACCCACCGACCCCTACCTCCCACCCACCAGGTGAGAACCACTAGTCTAGCAAATTTATTCATGC
CAGCAAGGCAGTGTGCGATAATTCAGGGGGAAGGCAGAACAGAAAAAAGTAAGTAACTGGGATGAATTAC
AACTCGGGTAATACAAACAAAAGCAGCAATAAAACTAAAAATGTTTCATCTGCAATTTTACAGAAGTTCT
CCAGACCATATTATAAATTAAATGTCAAGTCAGAGTGAGAATTAAGGTTATTCCTATATCTCTCGATCAC
CCCCAGTCCAAAGCCTCACTCCTCCAATCAGTTGAAAGAAACAACCACAGAAGGATGTCAACTGGGGTCC
CTGGGTGCATTTTAGGAGACTGTCTATACACTCCTGATATTGGTGGCAAAATGATATCCATTTGGCAATT
ATCTGGGACATCTTCACCAATAGTCAGAGAACTGTTCCTAAAGCATTATCCCACACCTCGTTTGTAGATA

FIGURE 3 (continued)

AGGTCATACATCACCATTTTGAATCAAACAGATTATATATTCCTCAAATCACTCCAGAAGATATAAGTCC
ACACTTGTGTTACATTCCTCTTCTAGGATGCATAATCATGCACTAAAATAACCCACTTAACAAAAAGTTA
ATCTACGCACCCACATGTCTATTAAAAATATAATGTTAGCAAAAGTTTAAAATGTAACAAAATTGGAATA
TTTTGCTTTCTTGTGGGACAGAATTATACTTTATCCTACTTATCAAAGATGTGAATTTGCCAGACTGTAT
TGATGATCTGATCTAGAGAAAATAACTCTATGGCTTGACTTCTCCCATAAACATCAGAGGAGATGATCTG
TCCAACACATTTCACCTTTCTACCCCTTTCTGCTCTTCTCCACTGCCGAGCTGCTCCTCCTTCTACCTCC
AGCTCCACAGGCCTCAGCTAGAGCAAAAGTACAGAAAGACAGCTGTATGGAAGCACAAGGGAAACACACT
GTTCTCCTTCCTTTGTGACAAGCACACATACCTGGGACATCTGGGCTGCAGTGCTTCCCTTTGCCCCCAT
GAAGACCATGGCCAGGGCAGAGGAGATGCTCATGGGAGAGAAGAATACGTTTCTTGAGTTGTCCTCTTCC
CCCAATATTTTAAATAAGCTGATGGCAAAAGTGCCATTTGCTTCACAGAGGTCATCCATCAGAGAAGGTC
TGCATCAAAGGCACAGCAGGGAAAAGCACATAAGCCAATGACTCCGGTAGCCACGCAGTCATTCATCCCC
CAGTCAGTGGACGCTGAGGTGGTAGGTGGAAGAACCACCCTCCAAAGACTTCCACTCCTAATTCCCAAAA
CCTGTGACTACATGATCTGCCCTGGCAATAAGGACTTTGCAAATGGTATTCAGTTAAGTATTTTGAGATC
TGAGATTATCCTGAGTTATCCCAGTGGGCTTAATGGAATCACGAGCGTCCTTAAAAGAGAGAGGCAGGAG
GGGCAGAGTCAGAGACAGAGACATGAGGACGGAAGCAGAGGTCAGAGGGATAGGGGCCACTGATGAAGGA
ATGCAACCTCCTCGAGAAGCCAGAAAAGGCAAGGAACAGATTTTCTTCTAGAGACTCCAGAAAATAACAT
TGCTATGCTGTACCATTTTGGACTTAGGACTTCCAGAACCATAAGATAATAAATGTGTGTCATTTTTCAG
CCACTAAATTTGTGGTAAAGTGTTATCACACCAATAGGAAACAAAAACACTGGTTTATTCATAAAATAGC
CAATCTCAGGGCCTATGACTTGTATCCCTCTTAGCAACAGGGGCACAGACACCCTGCAACACCTGCTTAC
TTCCTCCCTTGGTATAGCAGCAGCCAAAAGGTCTTTGTGCGGACGGGTGTGGTGCCTCACACCTGTAATC
CCAGCACTTTGGAAAGCCAAGGCAGGCAGATCACTTGAGGTCAGCAGTTCGAGACCAGCCTGGCCAACAA
GGTGAAACCCCATCTCTATTGAAAATTCAAAAATTATCCAGGCATGGTGGCGGGCACCTGTAATCCCAGC
TACTTGGAAGGCTGAGGCAGGAGAATCACTTGAGCCCCAGGAGGTGGAGGCTGCAGAGAGCCGAGATCAC
GCCACTGCACTCCAGCCTGGGCAACAGAGTGAGACTCCATCTCAGGAAAAAAAAAAAAAAGATCTTGGTGC
CAGGCACTGTTTTCAGCACTTTCCATTATCACCCAATAACACATTGAGGTCAGTATAGTTATTGCCCCAC
TTTAGAGATGAGAAGACTGAGTGAGGTTTAGTAACTCATTCCAGAACCCTCAGGTAGTCATAAACGCCTG
GCACCCACAGTTTGATTCCAGAGCCTGAATTCTTAATCATTACACAAAATCCCCCTATTGCTGCTAATTA
TCTTTCAGTTTAATGTCTCCAATATAATCTATAAAGAATGTTCTAAAACTTATATATGTAATTCTTTATC
AATAAAAACTGTATTTCTGTCATCACTTCCTGTGAAAACAGCTAGATACATTTCACCAAATTTGGAGGGT
TTGTTTGAGATAGGCTGGCCTGAAATATGAGGCTACTGGAAAGACAAAAAAAAAAAAAAATTACTTTTTAA
AGTGACTCCAAAAAGATGCCCCATTTTCCCCAAGAGTTGCTGAAACTGGGTTACGGAGTTGCAAAGAAAG
TCCATAGGCATGGATATAAAATATGAAGCCCTAATCTTGTCATCGAGGGAGCACTTTTAATTAGATGCAT
TGATTTTTGGATCCTCCTGGCTAAGAGGGTCTTAACATTCCCCTCAGCTTGAATTAACTTTAGACAACCT
AAACTTGACTAAATAAACAAACTAAACAGGCTTCCTCCTGCCTCTAGGCCCTTTCTTCCTTTTTCTTAAA
GCATTTTATTTAGAGAACTTGTCATTGTAAATTCTTTATCAGCCCCTTTGAGATGTAAATCTTTTAAAAA
AGCTTCTTGCTAGTTTTACATCCCAGGACAGTCTCTCAAAGACCTGGAAGCCATCCTTTTGAAATGTAAT
CATCAAGAAAGATAGCATCCCTATCAACCAGTTCTGTGGAAGGTAGGAGCCTAATCTAGGGGGGCACCTT
GCTTAAAGTGCTAAAAAGCTATTACAGTTTACTATTATTATAATTTTAGTGCATTATTATAAGTCCTACA
TTGTTGTTTATATCTATTAAACCCTATAAAAACGTGGGCTATTTCATAAAATATTGCAGTTCACCAACTC
ATCTCAATTTCCCTCAGCCTTTTTGTTCTTACAATTGAGAACATTTGGGAAAATAAAAGGACAAATCATT
ATCTATAATCTCATGATCCTACAGATATTTTTTCTATTATATTATCCTTTTTTTCATAAACATGTATAAT
TTTAACTGAAAAATGTAGTCAAACAAGAAAAATATGCTCCAGTTTGGAAAATTAGCAAATGAGCAAAATG
AAAAGTCCTGGAAACTCTATCTAGAGATATAAATTATCGTGCATGTGTTCATTTCTATAAACAGATGGAG
CCTCATCCAGTTTCCCAGCGGCCTACAAAGTGCCTGTTGCAGCAGCTCTGAAACTGTATGCCCTTAGTGG
GGGTCTTGGACAGGTCTTCTGGGTCTCTTAGAGCACAGGAGGAAAGGGGAATTGAGTGGCTGAGACAAGG
AAGTGGGGAACAACTGTATTAACCAAAGTATCTTCACTGTTGGATGTTTTGCTTCCTCCTAAGATATTTC
GCTTCCTCCTAAGATATTTTTCAACAGAAGGGTGTCTCTTACTTAAACAAAAAAGTGAGCTTATATATTT
TTTTAAAGTGTAAAGGCAACACTCTAAATATAGAACAACAGTCTAAAGCAGTGCAAATTCTTTAAAGTTT
AAAATAAATGTTAGTGCAGTTCAGAAAAAAACAAGTAGGGTTAGGGTTATGGTTAGGGTTCAGAAAACTA
AGTAAAATAAATGTGAACCAAGAAAACACAATCATGACATAATTTGCACAACAGTACTCTATACTTAAGA
GGTTGTTTATTATGGAACAAAATATTCCTGTTTCTCACTATCCTCACATCATAAGACCTCTCCAGAGCTT
ATACTAGGGTCTGCAGATGTTGGAAGGCAGAGTAGTATGTGCAGGCAAGTCCCGGGGTCCTCCACAACCT
CATCTTTCACTCGAGGACATTTCAGAGACTGGGAGGCAGGAAGGAATATTCAGACTTCATAGAACTGGGC

FIGURE 3 (continued)

CAACCAGAAGGTGGCACCAAAGAAACTTAAAGATGGAGAGAATTGGGTAAACTGGGTAAGACAGAGACAC
AAATAAATTTGGATTTGATCCAACCTTAGCATAAGAGCTTTGGACTCAGGGTGAAGCAAGCATGAACTTA
GGTTGGGGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTAGGTGTGTTTAATCATCCTGTCTGAACTATTGAAT
CAATAGTTTCAATAGTTCTGAATGAACTGAACTATTGCATCAATCTCATCTTTACATTTTAACTGCTCTT
AGTTGCAAACTGCTACTTCTGATTTCTTCCATCTTTCCTCTTCCTTCATCTCATGTCCCCACTTCCATTC
CTTTTCAACACTCAGGTGCTGGTCAGTATGTGGTATTTCCCATCAATATCTACCCTGCAGCCACAATACA
TGTGCACACACTCACACACAAGTGCACCCCCTTGGCCTCTGCTCAGGTCAGAAGTCAGGCAGGGGAGAAA
ACCAGGTAACAGAATGACTCTTCCCCCTGTCTTCCTGGTGTTCCAATCTCATTTGGACTTTATAGCTTTT
GAAAGGGTTGGAACTTTAAACAAAATGGACTTTACCCAATATTTCTAAAAAGCAATTAATTTTAATACAA
AATAATACTTTAGGTGCCAATGCCACAATTAGATTGTGTTATAAAAACACAGGAATCAGAAGTTTTTATT
TCCAGCCAACCAAATAAATTGGCATTAAACTAGTTTTTCCTTTTCAGGCAAACAAACAAAGACAGAGGCA
ATTAAATACTGTCCACAGGACTCACAGAAAAAGTGAGAGTCAGCCTCAAAAGCAAGCCTTACGTTTCCAA
GTATATGATATTGTCCTCCTCCTGGGAGCCCCAAATACCTACGAACTACCTCCTCCACTCCCCCATCCCC
ATACAACATCCAAAAGTGAGTTTATTCAAAGAGCATTTATGTAGAATGTTCACTACCTGTTTTGGGAGGA
GAAAATGAAAAATAAATGCGTTAATCACTGCCCAGAAGCTTACACCCTAAAGAAGACACACATATGGAAA
TGCGTAGTTTCAAGCCAGTCAGGTGCTCTATAACAGGATAATTTTGAAAGTGCTATGGAAATCCTCAGAA
AAAAACAAGTAAATAAATAAATAATAAGAAGAAAACCTCTACAGAATCCTGGAAAGACTTTCCAGAGAAG
CTGGCTTTAAAAGCTGGGCAGGCCAAGGTAATTTATAGATTCAATGCCATCCCCATCAAGCTACCAATGA
CTTTCTTCACAGAATTGGAAAAAACTACTTTAAAGTTCATATGGAACCAAAAAAGAGCCCACATTGCCAA
GACAATCCTAAGCAAAAAGAACAAAGCTGGAGGCATCACATTACCTGACTTCAAACTACACTACAAGGCT
TCAGTAACCAAAACAGCATGGTACTGGTACCAAAACAGAGATATAGACCAATGGAGCAGAACAGAGGCCT
CAGAAATAATACCACACATCTACAACCATCTGATCTTTGACAAACCGGACAAAAACAAGAAATGGAGAAC
GGATTCCCTATTTAATAAATGGTGCTGGGAAAACTGGCATATGTAGAAAGCTGAAACTGGATCCCTTCCT
TACACCTTATACAAAAATTAATTCAAGATGGATTGAAGACTTAAATGTTAGACCTAAAACCATAAAAACC
CTAGAAGAAAACCTAGGCAATACCATTCAGGACATAGCCATGGGCAAGGACTTCATGACTAAAACACCAA
AAGCAATGGCAACAAAAGCCAAAGTAGACAAATGGGATCTAATTAAACTAAAGAGCTTCTGCACAGCAAA
AGAAACTACCATCAGAGTAAACAGGCAACCTACAGAATGGGAGAAAATTTTTGCAATCTACCCATCTGAC
AAAGGGCTAATATCCAGAATCTACAAAGAACTCAAACAAATTTACAAGAAAAAAACAAACAACCCCATCA
AAAAGTGGGCAATGGATATGAACAGACACTTCTCAAAGGAAGACATTTATGCAGGCAACAGACACGTGAA
AAAACGTTCATCATCACTGGTCATCAGAGAAATGCAAATCAAAACCACAATGAGATACCATCTCACACCA
GTTAGAATGGTGATCATTAAAAAGTCAGGAAACAACAGGTGCTGGAGAGGATGTGGAGAAAAAGGAACAC
TTTTAAACTCTTGGTAGGACTGTAAACTAGTTCAACCATTATGGAAGACAGTGTGGCGATTCCTCAAGGA
TCTAGAACTAGAAATACCATTTGACCCAGCCACCCCATTACTGGGTATACACCCAAAGGATTATAAATCA
TGCTACTACAAAGACACATGCACATGTATGTTTATTGCGGCACTATTCACAATAGCAAAGACTTGGAACC
AACCCAAATGTCCATCAATGATAGACTGGATTAAGAAAATGTGGCATATATACACCATGGAATACTATGC
AGCCATAAAAAAACGATGAGTTCATGTCCTTTGTAGGGACATGGATGAAGCTGGAAACCATCATTCTCAG
CAAACTACCACAAAGACAGAAACCCAAACACCACATGTTCTCACTCATAGGTGGGAACTGAACAATGAAA
ACACTTGGACATAGGGTGGGGAAAATCACACACCGGGGCCTGTGGGGTGGGCGGGGGGGATGTGAGAGGA
ATAGCATTAGGAGAAATACCTAATGTAAATGACTAGTTGATGGGTGCGGCAAACCAACATGGCTCATGTA
TACCTATGTATCAAACTTGCATATTGTGCACTTTTACCCTAGAGCTTAAAGTATAATAATAAAAAAGAAA
CAACCCAAATGTCCATCAAAAACAGAATGGATAAATGGATTGTAGTATATTAGTATAATGGAATACAGAA
CAATAAAAACTGAAAGAACCATATCTATAAGTTCTTTAGTTTTTGACATGGACAATTCCCACAAATAATG
TATTAAAGGATTAAGCCACAGAGTAATACAGTATTATTCCATATACGTAAAGTTCAAAACCAGGCTAAAC
TAAATCATTCTGGATGCATGTGTAGACAGTAAAACTATGTCGTTATTATCATGAAACTCAGGAAGGTGGT
GATACAGAGGGGAGGGAAGCGGATGTGATGAGGGAGGAGGGTGTGATCAGTAGGGAAACACGGCCTCCAG
CGATGACAATATTCCAGTTATTAAACTGGGTGATGGGTTGTACTGCTGTTCTTTATAATTCAATACACAT
TTTAAATGTTCTTTTGTATTTATTCAATAGGTAATGAAACTTATTAAAACCACATATCAAAAAAAAAAAG
AAAAAAGAAAAGCCGGGCAGGCATTCCGTAGGTGGTGAAATGGGGGATGCAAATAATAGGCTGAGGAATT
AGCAGGTGCCAAGAATGTGGCAGGAAGACAAAGGGCATGGTTTGTGTGGTGCCCCTGGGGTGGGTTTCTA
TGGTTTCCTGTGAGCCACGTGGTAGTGAGATAGGACGGACCCTTATGCCACATTTAGGAGTTTGAACTTG
AGATTATGGTCTGGAAAGCCATGCATGGTTTTTAAACAAACGTCTCATATGAGTGCATTGGGGCTTTAGA
AAGATAACCCGGCTCAGTATTTGGTATGAAAAGAGGCTGGGGAGCTGGCGCGTAGGCCACCACCATGGGC
CAGGGACTGCTGAAAGCAGAGGGATTGTCTGCAATAGAGAAGTGGGGGCTGGAATTGCCAGGCAGTGACT

FIGURE 3 (continued)

GCTCACATAGGGACAGAGCACAGGAGGGCCCAGTCCCGAGGCGCCTAGCTGTTATAAATTCATACTCAGG
GTGGGTCGTGAACCACTGGAATTTTAAATGAGGAGTCAGGCTGGAATGGGGAATATGACTTGTTCCATTT
GAGATGCGTGGAACACACCATACCAGGTGAACCTGTAACAAAGACAGCCAAGGATGTTTGTAAACAGTTA
GGGACGGGGATGAGTAGACTGTCTAGAGCCAGAGACCTGGAGCCATCAGCATCCCGATTCCGAGAGGTTC
CATGAGAATGGATGAAACTACACAGAACATCTAGTGGAGGCACAAGGGAAGAAATCCACCTATTTCTGTG
GAATTTCCAATATCTGGAGGTAGTAAAAGGAAGAGACAGAGGAGGGCGAGGGGAGAGCGCGCGCGCGAAA
CGGAGACTGAGACCCAGCCATCAGGGTGTGCTGGGAGAACTGGGGAGACGAGTCTGCCCCTGCGAGTGGA
CCCAGGGAAGAGGGCGCGGTCTACGCAGAGCCCGAGGCAGGGAAGCGGGAGGGGCCCGGAGAGCAGCCCT
GGGTGAGGCCCTTTGGAATGGAGAGGTCTCAGGAGTGAAGCAGCAGCCAGAGGACTGAGAGTGTCTGGAA
AGTGAGGAATTGGTTAAAGTAACGCCGGTGGCTGCAACAGAGAGGGGCGTAGGTGAAGAAGCACCCCCAA
CCCCATCCCATTTGAGAGGAAGCAGACAATGAAGAAGAGAATATGAAAGATACAGAAAGATGAAGGCAGG
GGTGGAAAGAACGGAGGGGGGGGACAGGAAGGGAAGGAGAAGGTGCAACCAATAGGCTGTAAGCACAGGG
GCAAGCTTGGGCGCCAGGGGAGCAGGGACTCGGCGCCTCCCCGATCTGCCCCAGGCGCCACGGAAATTCC
AGGCCCCGCCACCCGCACTCCCGGAGCCTCCTCCGCAGCGGCGGCTCCTCCCACTCGCCCTCCCGGGGCT
CCCGCCCAAGCTTCCGGCGCTTCCAAACTCACTGCTCGCGTCACCCCCCGCTCCCATCCGGCAGCAAATC
ACAGCGCAGCAAATCGCAAGCCTAGAAACAGACGCTCCCTCTCCAGGGGCAGCTTCCTATTCAGGGCGGG
TCTGGGCGCACCTGTTCTCGGGACCCGGCCCTCGGCCTTCGCCGGGTCTCGCGGTGGGGCTTGGGACCCC
GGCTGGTGCCAGGGCGACCCCCACAGCCCCGCGACTCTCTTTCCCGGCCGCCTCCCGCCGTCATTCTCCT
AGTTCCTGCCCGCCTTTGCCTCGCTCTGATTCCTGCTCTGGCCTTCCTCCCTTCCCCTCTCTCACGCACT
CCAGGGAAGAGGTGGCCTCCGCGGGAACCTGGGCACCTCCGTGCCTGCCCCGCCCGGTACCTGGCAGAGG
CCCCCACCTCCTGCTGCTGCTGCTGCTGCCGCCGCCGCCGCCGCCGCTGCTGCTTTGACTATTCCTCCTT
TGTAGATGCTTCACGTCCGCCTTGATTGAGGGCAAGGCTTCCGGCAGATGACTCAGAACCGTTCGATTGC
TCTGGCTTGTGCAATCCCTGATTCTTTGGGCCTGTGTGGATGTCTGTGGGCACCGGAGAGAGGGCCAGTG
CCTGGTCCTTGGAGGGTGGTTTTTATAAAAAGTGTACACATTGGCTATTGTCCTTTTTTCACCGTTGATT
CACGTTTGACTCCACTGTAGTTAGACGTCCACCCAAACATTCTCTGAAATTGCTCCTGATAAGGATACTA
ATCATTTTCTAATTGCCTTGGCCAAAAAATACATCCCAGGTCTTATTTCATTTTGTTTGTTGGCGACATT
TAGCCCTTTCTTCTTTGACCTTCCCAGGATTTCCAGAGCACCCTTCCCTTCTTTCCTGACTCCTTTGCTT
GGTATCCTGATTCCTTTCCTACCATTCTAAGCCCTCTTCTTTTCATTATAATATGATCTTCTTGTATGAC
CTCCACTATATCCATAGGTTCATGTTTCAACTTTTAACTTATTTCTTCAAAATCTCTAACCTGTCTCGAG
CCGTAGATGTTACCTGTGTACTACTGGACATCTCTCAGAAACCTGGGTGTGTCCCTCCGCAGTTCTTTTA
ACTAAATGATCAACAGTCCTGTTACTTCTATCACTTTTGTGTTCCTCCTGTCCATACTCTGTCACCTCTA
TCATGTCTCATGTCTCTCCTAAACAATTAATTTTCCTACCTACAGTTCTGATCCATGCCAACCTATTGCC
TACTCTGAAGTTCAGGTAAACATTCCAATTCTAATTATTTTATACCTCAGTTTAAAATCCTTTATAACAT
CCTCTTATCCAAAAAGATAAATTAGAAACTATTGAGCAAGGAGTGTAAGCCTCTTCACGTCTTGATTTCT
CCCTTCTTTTCTTTAGAGCCATAGCAAATTATTTACATTCCTTCATATCCTCTGTTCATATACATGGGGT
TCCTGGCATGCAAGCTTGTCTTTCAAAATTCAGTTCAAATAATGTCTCCTGCAGGAAGCTCTCACAGAGC
TCTCCAGTTTGGGAATTCTGCTTTTAAAGATGCACATTCCCACTCTGCACCCCAAACCAATTAAGTAAAG
ATCTCTTGGAGGAGGGAACCCAGCAGCAGTATTTTGTAAAACTCGCTCAGTGATTTCCCTGTGGAATCCT
AAAAGTAACTGTTCCCAAGAACTCTCCTCAATAAGTCTTGGTGCAGGATTCACCCCCATCTTTTCTCCAT
GACTTTGAAACCCCTCTCTCTAGTGGCTACAGACTCACATTTGAACTGTGCCCAAACTTACCGGCTCTGC
CAGTTGAAAATGCCAAGGTCACTTCCCCATTGTGCATCAATTTCTCCTTGTTGGTCAGAACTAGATCCAG
ACTTTGGGCCCCACTTTGTCCATCCACTCCTTTTCCTCTTTGACCAGCAAAACAGATTAAAAGATGAAAA
ATGCTTGTTTTCCTCCGTGAAACTTCCAGCAAATGCCTGGTGGTTTGAAGTCCTTTACAAAGGATATAAT
TTGGCCCCTGGGAGTTTGGTTGTAAACACAGATATCCCATGTAGGAAACACAGTGCGTGCAGGTGCAAAG
AGGCACAAGATAGCACCATGAAAACCATGACGTATCCAGGCCTGCAGTGGTACAGATAGTGTGGATGAGG
CACTGCAAGACAACGTCTGATGTGTCCACAGGGCCATGTCGTGAAGGCCATGTGGACGCTGTTGGTGGTG
TTTCTTCGTTCCCTTGTGGACTATGGGGAAACACAAAAGGATTTTAAGCTGGGGAGAAACATAATCATAT
TTGTATTTACGAAGGTCCCTCTGGCTGCAACATGGAGTATATTGTAGGAGGGTACCATTGCCTGCAGTGA
GGCGTTAAGGACGCAGCATGGATGAGAGATGAGGAAAGCTGAAATGAAACAGAGGCAGGAGAAATGGAGA
GGAGGACATGGCCTTGAGGAATTTCCAGGACATAAATTTGGCATCACTTCTTGGACCATGAGAGGAAGAG
GGAGCAGGAAGAATCAAAGATGAATCCAAGAATGAACAAATCTAATTTTTGAAATAATGCAATGAAAAGT
AGAACTGGTCTGTTTTCCTAGGTAAGGAATTTGTCTGCAAGTCGATATTCACGAGGATTAATTGTATTTA
TTTTCTGAGTATGGACAATTTAAATGCTGGGCCCTGAAGGGAAACCCATCTCTCAGAATAACTAAAGCCC

FIGURE 3 (continued)

AATTTCAGAGTGAGCCTGAACAGGCTCCCCACTCCACCCTGGCCCACTGGGGACACAACAGGTAACTGAT
AAGGTTCCAGAGTATATAATTCAGTGCCTCAGAAACTGTCCTCAGCCTCATCTTCTGTCTTCTTGCCTCA
TACCTAACTTCACATCTCTTCAGTCAGTACTAGGGAGTATCTGCTGGTTCTCAACTCCCGACTCAACCTT
GACCTAGTTTTGTCTGACTCCCTCGGCTCCTGACTTTGTGGACCTCAGGAAGGGCACACTCCTAGGCTAG
TCTCAGGTTGAGCTACCACCGTCTCCAAATTAGACTTCCACTTGTCAAGAAGGAAGTAGAGTCCAGGCAT
AATTGGAGCTTCCTGGGGTGATTCGAGGTCTCTGTACTCCTTGCTGTAAAATGCACAAATACTCCACCTT
AAAGAATCTCACGGGGCAGGGCACAGTGGCTCATGCCTGTAATCCCAGCACTTTTGGAGGCCGAGGCGGG
CGGATCACCTGAGGTCAGGAGTTCCAGACCAGCCTGGCCAACGTGGTGAAACCCCGTCTCTGCTAAAAAT
ACAAAAATGAGCCAGGCGTGGTGGCAGGTGCCTGTAACCCCAGCTACTAGGGGGCACTGAAGCAGGAGAA
CTGCTTGAACCTCGGGAGGTTGCAGTGAGTTGAGATTGTGCCACTGCACTCCAGCCTGGGCAACAGAGCG
AGACTGTCTCAAACAAACAAACAAAAAACAAAGAGTCTCACCGGAGTTCCAAAATATCCTTCAGTGACTG
ACCATATACTCTAGCAAAAGTTACTTCATATATGCCCGGCCACAGCTCTCAATCTCCCATGAGATTCCCA
GCAATCTTCCCTGGTTTTGAGAAAGTGTAAAAAAACACAAAAAGCAAAAACAAAACACACTTGCTTCAGC
TAATTAATGCTAGAGAAACAAACATAGCATCATAAAATGTAAGCATTTGAAAGAACCATATTGTTGACGC
TGTTCCTTATATTTTGCAGGAGAGGATGGTGAAATAGAGGTAGTTTGTGTGATTTGCCCAGAGTCCCATG
AAGAATTCACAGAAGAATTGAGACTACAGTCAGTATGGCCACATTCCCAGAGAACTGCTTTTTCTGCCAT
ACCCTGTGGTAATAATATTGTCACAAGACAATTGGACAGTGTTTCACATATTCAGTGATGGAAGAAGAGT
TTAATTGAAATAAATAAATGTCAGGAAAAATTAATTCGATTGTGATAACACTTAAGGAATGGAGTGTTCA
CTCTCTAGGAGAAGTTGGGCTAAATGATGAAATGGAGTGTCCGTGTATGTGATCTGTGGTGCTGTTTTGC
TGTAGTTAATTCCTATTTTTAACTTGAAATGTGTTCTGACTGCGTTAGTGCCAATTTTTTTGAGACCGGT
GTACCTATCCTATCAGGTACATTCGATTTACACAAGTACATTCTCTTTTCAGTTCTCCCACCACTTCTCT
TTATTCAAACAATTAAAACCTTCTTGAATATTATTTGGTTAGTCCTTTGAGTTAATGAATCAATTTTACA
GGATCTGCTTCTGTCATTTTTCATTAACATTCCCCAGACAAATTTGTACTGCTTACTAACAGCACAATCC
TAAATTCAAAAGATTACTGAGTTATAAAGTGGATGTCTGGACAATCCAAAACATAATGGCTGTGGTTTGG
GTGTGGATTTTTGTCTCCACGAAAACCCACACTGCGATTCAGTCCCTGCTGTGCCAGTGTTCCACTTAGG
GAGAGGTGTCTGCGTCATGTGGGTGGATCCCTTGTGAAAGCCTTGGTCCTGTTCTCCTGGTAGTCAGTGA
GGTACAATTAGCTCTCATGGAATGGATTAATTCCTCCAAGAGTGGGTTGTTATAAAGTAAGGTTTCTCCC
CATGTTTGGTCCCTCTTCGCATGTGCCTGCATCCCCTTTGACCTTTCCCTCATTGAACCTGCAGGTTCAA
TGAAGGTTCACTGCAACCTCCGCCTCCTGAGGTTCAATGTCTTTTGACATAGCACAAAAGCCCTCTCCAG
AAGCCTGGGGATGCCAGTGCCATACCTCTTGTATATTCTGCAGAATATGAGCCAAATAAGCCTTCTTTCT
TTATAAACTACCCAGCCTCAGGTATTCCTATATAGCAACACAAAACAGACTAAGACAATGCTTATATGAA
AATGTCTAGATTGTTACCAAGACAAATGTAAGCAATGAAACATACATGTTGTAGAGCCTCTGCTGATCAA
GGGTATGGAGAACCCAGTGGACCTTAATGTGAAAAGCATTACATTAATATGCCTGGTATTGTATTTCAAG
GAACTTATAAAAGAAAAAAAGGCTCCTGATATGGCATTGCCTGGAAACTGCCATTAGTCCCTCATTAGTG
AATCGTCAGTCTCTCCATTAATTTGAAGGGGGTTAAGGGGAAGTATTAAGTGACAAAGAATTTGGAGGGA
ATTAGAAAGATCTCTTTGGTTTCTAAACGTATCTTTTCGTGCTTTGATTGAATGTGTTGCAGATAGGAAA
GTTGAATAGGAGATCCCTGATAGCCTCTCAGATTTTAGCTTATCAATAGAGTTACCATTGATTGTTGAAA
CAGTGTGAGTTCCTGCCACTTGTTCTAGTGTCCTGTCTGGTTCAGCATTAATCTCAGAATTTTCAGTTTT
TAATGGAGTAGTTTTTCTAATAGCTGCACACCCTCAAGCCAGAATGTGTTTGCTAGATCCACACTGTGGA
CTTCAGTCTCCTGCCACACTCTTTCATAATAGTGGGAGAGATGCTTATTCAGTTACATCAGGCAGTGTTC
ACTTTGCAAACAAACTACATCAGAGATTTGAAGAGAAGAGAATTAATACAAAGAATTATTAAGTAATAGA
TTTTTTAAAAATACTGTAATGGCAGCAGATGTAGAAGGTACAAAAGAGAAATTGTCACTTCATGTCTTGG
GGTAAGTGGAAAAAAAAAGAACTAAGGACTTAGGAAAAGACATAGGTCATAGACTGTATTATGTCCTCAC
AAAATTTTTATGTAAAAGCCCTAACCCCTAAGATGATAGTTTCTGGAGATAGGGCCTTTGGGAGTTGATT
GGGGTAAAATAAAGTCAGGAGGGTTGGGCCCTCTTGAAGAAATTAGTGGCATTAAAAGAAGAAGAGATAA
ATTGCTCTCCCTGCCATGTGAACATAGCTAAAAGGTGGCCTTCTGCAAACCAGGAATAGAGCCCTCTTCA
GAAACCAAATCTCCTGGCAGCCTGATCTTGGACTTCCCAGCCTCTAAAACTCTGAGAAATGTCAGTTGCT
TAAACTGCCCAGTCTATGGTATTTTATTTTTATTTTTTGAATCAGTGTCTCACTCTGTTGCCCAAGCTGA
AGTGCAGTGGCATGATCTTGGTTCACTGCAGCCTCTGCCTCCTGGGTTCAAGCGATTCTCCTGGCTCAGC
CTCCTGAGTAGCTGGGACTATAGGCAGGTGCCACCATGCCCAGTTAATTTTTTTGTTTTTGTTTTCAGTT
TTGTATTTTCAGTAGAGATGGGGTTTCACCATGTTGGCCAGGATGGTCTCTAACTCCTGACCTCCGGTGA
TCTGCCCACCTTGGCTTCCCAAAGTGCTGGGATTATAGGCATGAGCCACCACACCCAGCCTATGGTATTT
TATTATACCCACCTGAGCAAACTAACATGACTGAATGTCCCAAGGCTGATATTCAGAGCTCTTTGAAGGT

FIGURE 3 (continued)

GTGGCTGCCACAGGAACATGCAGTCTGCAGTGGCTATGAAACTTGTCAGATGGCCAAAGCTGGCTTACGA
GAAGCCATATGTCCTTGCTGGAGGGTGTGGGCAGGCTGGGGCTGGACCATAGAAGCAAATGCCTGGTAGG
GATATAGTTGCCAGAGGTTGCATCTTGACCAAATGCAGAAATGGCCATTGTGTGGAGAAAGCATTCCCTG
AGAATGTGGCTACAGATGACCAAGTGAGCTGCTGGGTGCCTACACTGAATAATCCTAAGAAGATCAGAAT
CCAGAAAGTGCATTTCTACTTCTATCTTCTTACAGTGTCTCTCCAGCTCCCTCTATTGGCAAAGCTGAAC
ACTGGGCCAGTCAGTCAAGTTCTTGTTACAGGATCCAGGTTTACTATCACAAAGTCCACAAAGGTAGATT
TAGAGCTGATAGACAATAAATTGATATCTGGCACAGCAATGAATGGAGTTCTCAGGCAAGCCTGTCATTA
AATCTGGATGATAACTACTGAATCTGTCTCTTTTCCTGATCCTCTCCAGAATCCTTCATCTCAAGGACAA
TATCTAAGGAATTCACTGGTAAAACATTTTATGCTTGGTCACAAGCAGCTAGAGAAAGCAAACTACTTCC
GGCCTGGTGCGGTGGCTCATGTCTGTAATCTCAGCACTTTGGGAGGCCGAGGTGGTGGATCACGAGGACA
GGAGTTCAAGACCAGCCTGGCCAACATGGTGAAACCCCGTCTCTACTAAAAATACAAAAATTGGTCGGGA
GGCTGGGGCAGGAGACATGCTTGAACCCAGGAGGTGGAGGTTGCAATGAGCTGAGATTGCACCACTGCAC
TCCAGCCTGGGTGACAGAGCGATACTCTGTCTTGGAAGGAAGGAAGCAAGGAAAGAAGGAAGGAAGGAAG
CAAGGAAGGAAGGAAGGAAGCAAGGAAGGAAGGAAGGAAGGAAGCAAGGAAGGAAGCAATGAAGGAAGGA
AGGGAGAGAGAGAGAAAGAAAGAAGAGAGAGAGAAGAAAGAAAGGAAAGAAAGAAAGAAAGAAAGAAAGA
AAGAAAGAAAGAAAGAAAGAAAGAAAGAAAGAGAAAGAAAAGAAAGAAAGAAAGAAAACTACATCT
GAAGTCAACACTAGTATTGGTGGGAGAGGAATTTTATGCTGCATTCCCCAACAGCCACTAGATACGCCAA
TCAGGTGTGCATGGTCCATGCTATGATCTGTGAGTATCAGATCAACGTCAGCTTGTTCAGCAAGCCCTCA
GGACTGGAAACCTCCCTCAAGTCCTCTGCCCCCTCCATCTCCTTCAACACAGAAGCTTCAGCTCAGGAAA
GGAAAGGCCACCTTTCACATGCAGAAGCGCATCAGCTTCTGGAGGGGTACTTCATGAAGGTACTGCCTCC
ATCTTCTCAGTCTCCAAACCATCCCTTGCTTTGGACCTCTCCTTTTCAACTGTGGCCCTGCAGCCCTCTT
TGAGAAGAGGGATGCAAGAGCCTTAGAGTTCCCACTTATTGAAGCATAGGAGGAGTGAAGGCTCTCAGGA
CCTCCATTCAGGACTCCTGGAGGGGGTAGCAATGCTTGCAGAGTTCATAGCGCCCAGATGCACCTGACCT
TAGCTCCATATCCCAGGATGCTCATCCCTGGATCCAGGATGATGTGCTTTTGGTGCCAGAAGTTTCTGAG
TTCCACTTTTCAGATGGGATAACACAGCCAAAGAAATCAGACTTCATCTTAAAGGGAGACAGGTTTCTGG
TCCCTACTCTTCCTGCACTGTGCTGACAGCTGCCCTTCTGGTAGGAGCTGATATAGGTAAGTTTCACAAT
AACAAGAGGAAGAGATTACTCATGGCTTTTCTGGATGTACCAGGCTTGTTTGAGTAATTTTCCAGTGTTT
GGCATTACCAGACATTGGATCCACATTCTACCTCGTTGCTAGCTACAAGAACTTGTTCAAGCTACTTAAC
TTCTGAGTCTCAGATTCCTCATGGGTTTATTATCACTAAGGATTAAATAATCTATGCAAAATGTCCAATG
CAAAGAAGGTATTCAGTAAACATATCTGAGGAGGTCAGATCAACTTTTTTTCCTAGAATTCAATTCTAAA
TGGAACTCACTTTGTGGATACTTACAAGAAACACTACATAGTGTAAGGGAAATGTCTTAGTGCAATTTCA
CAAAACACATGGAATTATTATTTGGGAGGCTGGACCTTTCACGGAATTGTAGCTGTTTTGATTGTCTCAT
ATTCACCTTGTTGGTGAAGGAGGGATCTCCCCCATTAAATAGTAGGAGATAACTAGACACATGGCATGAC
ACACTGGACAGATGAAATTGGCGGCAGTTTATTAGTCACAACTGCTCACAGGGAGGGAGGTCACCACATG
CCATGCGGGGTCACAGGAGAGTTGCATTTGGGAATAGAGTGAACCAGTAGGGGCTGTGGAAGGCAGGCTT
TGCAGTAACAAGAGGAAGAGGCGATTCCTGGCTCCTCCAGATGTGACAGGCTTGTTTGAATAATTTTCCA
GGCTGGAGGGAAGTGAGCCACGTTGAGACCCAGGGAGGGTACAGCTGACTGCCTGGTAAGGGAACTTAGA
AGGGGGAAGAGCCTTCCTGCTCAGTGGGTGAATAGGGTGCACATATCTGACAAGAGCAGGGGACTTCATG
GCCAGGCCTCTGAGGCCCTGAGAAGCCCATAGATGTCAAGGCAGCACATGAGCTTTCAGGCTTTACAAGA
CAGAAATAAAATAGTGAATGATAACTCTTCAAAGAGAATATGACAAACAAAATTTCACAAGACCCTCTAG
GAACAATATGCATATTGTTATCTCTATGTTTTATGATTTACATGGCTAAAGTCTGATTATATTATATTTC
TATAACAGATAAAACCATTATCATTCATTTTCATAATTCATATTGAAATGATTTGATTATCCTCATTCCA
GGAAAGAAAAAAAAAAAACACCCTCCTGCTTGGATACTTAGAGGTTACTCCATTTACACTCCCCACTCCC
ACCTCTTACTCCACTTGACTGGACTATCCACAAGGCAGTGCAAAGAGGTGTGTGTTTCCCTGAAGAAGAG
GGTGCCACCCTGTTGCTCCTGGCTGTAACACTCAGAGGCTCTCTCTGCAGTGGAAGAATCATATGGGCTG
ATTATTCCCCACCTTTCAGACTTCTTTCCAAGTCCAAGTGTTGGGCAGAGGAGGAAGAGGAATGAGAGTA
GCAAACCCGGCAACCTCTGATACTCCCTCTTTCCTCTCTCAGCCCACATATAATGTGGATGTCTCCTTGT
AATCTTCAGTCTCATTCTCTCCCTGAAGCTAAGTAGCTGGCTTTGGTACAAAGGGAAAAGTTGGCCAGTT
ATGGAAAGAAAATATGGGTTGTGTCAGTGAAGTTCTGAGGGCTCAGGGTCTTTCTGGCTGCAAGGGGGTT
GATGGAATGTCTTTTTAGCTGTGCCCTAGAAAACAATATAACTCTCCCTGTTCAATCTAAATCATCAGTG
TGTTCCCTTATCACTGATCACAGCAGTTGCATTTCAAGCCTGTAAACCATACAGTATGGCAATACCAGTG
AGGGAGACAGCTAGAAATTTTTAAATTCAAATTTTAACGCTATTTGTGAAAAGAAAAACTACCTAATATT
AACAAGCAAAAAAACCTGGAAGAGATTATTTCATCTAGAGAGACATCACAGATACTTGATAAGGGAAAAG

FIGURE 3 (continued)

CTAAAGCTAGAGAAAAGGTCTACGAGTTGGCAATATTTCCAAAGAAAGGTTTTAATGTTTGCATAGTTGT
TTAGAGAAAAAAGGACTCCTTTTTATATTTGACAGTTTTGTAAAGAACTGACTATAAAACTGTTTAAAAT
ATTATCGAAATAGAATAACAATATATTTTCACCTTTAGTTTTATCAGCAACCCAGGAGTTTACACGTGTT
GTGGACTTCTCTGTATCATTCACAAAGTCTAGCTGTTTTATCGTTGCTTGGTAGAATTTGCCACAGGAAT
CTGTAAAACCCTAGGAAAAACCAAAAACATAATTTCACAGCTACAGAAACAACTAATATCACTGGCTTAC
TTCTTCATTGTGCCACATCAGAAAATCAATAATTTTATGATTTACCATATATAATTTGCAAATAAAGATG
AGGAATTAACCTAAAGTCCAAATTCTTTTCAGCTATTCCTAATCTTAGCTTATAAACTAAGCAACGCGGT
GGGCTGCATATCAAGTGATTTTCATCAACTGCTGGATCCTTCATGAGAGTGGCAGTACACCCATCAATGA
GATAATTTAAAACACTGAGAAATCTCCAAGAAGACATAGAAATCCTTAATAGGTAAGTACCTAATAGTGG
ACCATCAAGACACATAAGGCAACAACTAATAGAACTGAAAGGAGAAATAGATGAATCCACTATTATAACT
GGAGACTTCAATATCCCTCTATCAGGAATGAACAGATCCAGCAAGCAGAAAATTAGTAAAGAACATAGTT
GAACTCAAAAACAACATCAAGTAACTAGATATAATTGATATCTATTGACTACTTCATCCAACAAGAGTAG
AATCTATATTCTTCTCAAGCTTACATGAAACATTTACCAAAAGAGACCACATTCTGGGCCACAAAGCACA
ACTTAGCATATTTAAAATAATAGAAATCATGCAACGTCTGCTCTCAGACAATAACGAATTAAACTAGAAA
TCAATAAGAGAAAGATGGCTGAAAATTCCAAAAGTACTCGGAGATTCAATAACACACGAATCACAGAAGA
AATCTCAAGTGATATTAAAAACAGTTTGAACTAAATGAAAGTGAAAACACACTGACAACACTAAATGCTG
GTGAAAACGTGGAGCAACAGGAACTCTCATTCATTGCTGGTGGGAATACAATATTGTATAGTCACTTTGG
AAGACAGTGTGGAAGTTTTTTATAAAACTAAAAATATGATCCAGCAATCATGACCCTTACCATTTACCCA
AAGGAGCTGATAAAACCTGCACACAAATATTCATAACAGCTTTATTCCTAACCGGCCAAGGTAGAAACAA
GAAAGCTGTCCCCCATGACTGTACTAGGGGATGTTAATCACAGGAGGGACTATGCATGTACCTTTTGCTC
AATTTTTCTGTGAACCTAAAATTGCTTTAGAAAATAAATTCTTTTTTTTTCTTTTTTACAAATGGTGACT
ATAGAAGCTGTCACTCCTGTAAATTATTAAATTTGTTGAGTGAGGATTAACACAGCAAGTGCTATATTTG
CCTCTACATTTTAGAACAACAGACTATAAATATGAGTCTGTTGTTCCATAAATTACATGGGAAACATATA
CAATCCTAGACCAGCAGTGTCCATCGGAACTTTCTGGGATGATGAAAATGTTGTAAATCTGCAATGTCCA
GAGCGGTGCCACATAGGCTATTGAGCACTTGAAATATATTAATAGCTAGTTGGACTGAGGAACTGAATAA
TTAATTTCATGGAAACCTTATACTCATGTACATAATGCATAGCATTATGGGTGTTTCAAACTATGATCAA
CTTTCCAAAAAAGTTCAAACTATATTTAGTTAATATATTCTGTAGAATTATAATGATCTTAACAGAAACC
TACACTATGCCACATAAAAGCAGAACATTTGGTGGAAATTAAATGAGCTGAAACAACTAATTTATGAACC
ATGCATTATAGAATTGTTTCCCAATCTTTCTCTCAAACTGCTCACAGCTAAATATTTAATTTCCCTTTCC
ATAATTTTGCTTTTACTTTGGAATTTTATACTTCTGTATCAGTATGGCATGGAGAGGAAATGTGACTGTA
GTTAGGAACACAAGTTCTGCAACTTACTAGTTGTGTGACCTTCAAATATTTGCTTCCTCTGTTTATGCCT
CCATGTTCTCTCCTGTAGAACAAGGAAGCAGTAATAGCTACACCTCACAAGATAACTGTGAAGTCCTGAT
GAAATATCACCTTTTCATGTAACGTTTTTGAATTCTCAGTACCACGTAACTGATCGATGTACACTATTTC
ACTTAATCCTCCCATAATTCATGCTTTTCCAAAATTGCTGCCTCTGCCTATTTTTCAGTGGTTTGGAAAT
TATTTAAATCTCTCAGTGTAAGAAAATAATCTGAAGGCAAACTGATGAATCACATATTGATGACTTCTTG
CACGCCTAGGTGATCTTTCCATCTGTTAAACGTGTTTTTAAATAACTGTCTGCTATTTTAAGTTACTATT
TGACAAAGTGTGGCAAATCAAACAAAAAGAACATGTAATTATATATTGCTATTGGTATGGGATTCTTGAA
AATAAGAATAAATAATAAATTAATCTGAAATGGTTTACAAATATTTCTCATCTTTTTAATTTATATTCCA
ATATCAAAATAACATTTTAAATATCAATGCTTTTCTTTCAAAATATCCACCACGAATTGATATTTGGTTG
TTAACATTTTGGTTGTCTTTATATAGAAAACTAGTAAGCTAGTAAAAAGATGGCAATAAACTAAATAGTG
CTAAGACTAGTAAAATAAGTGAAGTTGTAAAATCACAATATCATATACAAATCTTATAAATATTTCACTT
TTATGTCTTACCACCTTCACTTTATACCAATCTGTTTGCAAACAATTAATTTAGAGTCGAAAGCAAGTTT
GAAAAAATACATATCACAGTAAGAGAGATATCCTCTACAAAAATAATTCTTATAAGTCAATAAGAAAAAG
ACATACAACCCCATAGAAAAATGTGTAAGAGGATATGTAAATAGGCAATTCACAGAAGAGATAGAAATTC
TCAATACACATAAAAGTGTTTAATCCCATTTATAATCAAAAGTTTTTATTTTTTTTTTTTGTTGCTTCTC
TTGTTTTGTATTAACCCTTCCCTATCGCATATGTTGTAAATATTCCATCTCAGATTCTTTTTTAAAAACT
TTATTTTAGGTTCACGGATACCTAAGCAAGTTTGTTATATAGGCAAATTTCATGTTTCAGGGGTTTAGTA
TACAGATTATTTCATCAACCATGTAATAAGCCTAGTACCCGATAGGTAGTTGTTCAATCCTCACCCTCCC
CACACCCTTCTCCCTCAAGTAAGCCCCCATATCTGTTATTCCTTTCCTTGTGACCATATGTACTGGATGT
TTACCTCCAACTTATAAGTGAGAACATGTGGTATTTGGTTTCCTACTCCCGTATTAGTTTGCTTATGATT
AATAGCCTCCAGTTCCATCTCTGTGGCTGCAAAGGACATGATCTCATTCTGTTTTATGGCTGCATCGTAT
TTCGTGGTGTATATGTACCACATTTTTTTAATCCAGTCTACTATTGATGGGCATTTAGGTTGATTCCATG
TTTTTGCCATTGTGAATAGTGCTGCAATGAACATATGTGTCTTTATGGTAGAATGATTTCTATTCCTTCA

FIGURE 3 (continued)

GGTATGTACTCAATAATGGGATTGCTGGGTCAAATGGCAATTCTCTTTTAATTTTCTTGAGAAATCACCA
AAGTCCTTTCCACAGTGGCTGAACTAATTTACATTCCCACCAGCCGCATGGAAGTGTTCTCTTTTCTGTG
CAGCTTCACCAGCATCTGTTTTTTGACATTTTAATAACAGCCATTCTGAATGGTGTGAGATGGTATCTCA
TCATGGTTTTGATTTGAATTTCTCTAATGATTAGTGATGTTGGCAATGTTTTCCTAGGCTTGTTGGCCAC
GCATATGTCATCTTTTGAAAAGTGTCTGTCCATGTCCTTTGGCCACTTTTTAATGGAGTTGTGTTGTTTG
GTTTTTGCTTGTAAATTTAAGTTTGTTTTTTTTTTAATAGATTCTGGATATTAGACCTCTATCAGAGGCA
TAGTTTGCAAATATTTTCTCCATTTCTATAGGTTGTCTGTTTACACTGTTGATAGTTTCTTTTGCCCTGC
AGAACTTTTCAGTTTACTTATGTCCCATATCTCAATTTTTGTTTCCGTTGCAATTGCTTTTGGCATCTTT
GTCATAAAATATTTGCCAAATCCTGTGTCCAGAATGTTATTTCCTAGGAGGGCGTAGAGCAATCTTACTT
CTCCCAGGAACCACAACTGTGGCCTCTACTGGGGCTGTGGCTTTGGTGCTGGTCTGCTACAGGGCCCAAG
GCTTGTAGAGGTCCCCCTGGACTCCAGAATTACCCCTGGAAAACGTCCAGGTGGCACTCTGCCCCAGTCT
AAAAGCACAGTGGGGAAATGCGGTGGGGACAGGAGGATTCTCCCATTCCCAATCTTGCATAGGTCCCTGT
GGACAGTGTGAATCCCACTAGGAACTCTCATTCACTCATCCTTCCCCATTTTGTAGGGGTCCTCCTGACC
GCACTGATCCCAGACAGGCTGGTGCCCAGATTCATTCCTGTCTGCTCTGTGTGTTCCCCTGCTGCCTAGA
TGGATCTCGACATGGTTTCTCAGATGATCGGCTTTCAGGGTCAGTGTTCACTACCCCTTTTGTTTCCTCT
CGGTGACGCCAGCATCAGGAGCTCCTTTTAGTCGGCCATCTTGGCCCCACCCTTCCAAAAGTTTTAAAGG
TTAACATTATGCAGTTCTGCTGATGGTGGGTGGAACTGAGGATCCTATAAATACCCCCTGCAGAATGTAA
ATGGCTACAAAACTGTGGAGAGCAATTTGGCAATATTTATGAAAACCTCAAAGCTTCATTCCCTTCCTCC
CTTCTACAAATCCATTTTAGATAGTAACTCATACACATATGCACAAAACTGTGTAAAGAAATACTCCTGT
CTGTAATGGGCCAGAGTAAATAAGCTTAAATACTCGTCAATGCAAGAAAGGTCTATTATACCATGGTACA
GCCATACTTAGGAATACCAGACAAGGGTTAAAAAGAGTAATACAGATCCACATATACTGAGATGGAAGGA
ATTTAGGACATATTTTTAAGGAAAAGCTAACAAAGTATAAAACAATATGCATAGTACAATAACATTACAT
AGGAGAAAAACTCATGAAGCAAAGTTTTTATATGTGAAGGAGGAAACATCAAATCTATGAAAGCTCTAAC
GTTAAAAAGGGGAGTTGTGGCATAAGAAAGAAGCTGATGACATCTCTTGGTTTATATGTGTTGTTTGTGT
TTTTAAATAACAAGAAATTACTTCGGTACTTTTCTTTTCAAAAACTAGAAAAGTCATGAAAGCATTGTCA
GCGAATGCAACCAGTGTAATTAGCCAAAATTAGTTTTAAAAGATTTTCATTGCTGAAACATCTAGTCAAA
CTATTTAATGCATACATTATAGTGTCATCATGCATAGAAAATTAAAAATATCTGCAAAGCAATTACGAGA
AACAGTCATTTTCACCACATCTTTGTTTTGGCTGATTCATTTTCAACTGTGTTACGCTCTGTGTCAGTTC
TTTTATGAAGATTATCTCATTAAAGCTTCACAAAATTCTGAACGGTATTTGCTATATAGCCTGTGCTACA
GATGATCAAACTGAATCACAAGATGCGTGTGAGATTCGTGCGTGGAGTTCTGAGTTCAGGACCACCTGCA
GGAATTCATAGCCCATATTCATTCTCCTACTTCCCACCACATTGCTATCTTTATTTTCCTAATAAACAAG
TATGACTTACTGTGAGGAAATCATAAGACTTTTCTCCAAAGAGCCCGTTGGCAGTTCTAAGCACATATTC
AGTGTCAGTTCTGTTAATTGCAACAAGAAGTGACTGAAAACCTCGATGAATATCTCCATCTTCACCTCCG
ATTTTACTAAAACAAAGTGCCTGAAAATAAAATAATAATAAACATACACATTCTCAGTATTCTGTGACTT
CAAAATATAGGCACAACAGTAAACTCAGCAATATGAGATTTACAGATGCTTACTACAGCTTAAAAGATGA
TCAATCTAATAAAAGATAGAGAGTGTCTCAAAAGCAACCCTGTCTGCCTACCTATGCCTCTTCTCAGGCC
TCCCTATAAGCACATCCTAAAAGAAACGAATGTTATCTAAGTATTGGTATAAGTGGATATGCCTTTTGCA
AACCCTAACAAAATGACTCGGATTTCTTGTGCTATTTATGATACTTGGTCTAAAAACGCAGCTGCCAACC
ATGTGTCCTGTCTCTGCATACACATGGTGCTCCTGACACTAAAAGATGGAGTCTCTCTCCCCTTCTTCAG
AATCTGGGCTGGCCATGTGACTTGCTCTAAACAGCAGAATGCAGAACTGGCTCTGTTCCAGGCTTAGCCC
TTAAAAAGTCTGGCAGCTTCCACTTTCCCTCTCTTGTAACCCAGCTACCGTGGTCGAGAAGCCCAAGCTA
TCCTGAGGAAAGACCACATAAAAGGAGGAATGGAAAGACTTGCTTTTAGGGAACTGAGGGCCCATCCACT
AGCCAGAACCAAGGCCCAGACATGGGAGTGGTATCTTCTTGGACCTTCTAGCCCAGTTGCCTGCAGAAGC
ACCCACATGAGTGACCCCAGGTCACCAAGAAGGTCAGGCCTTGAAAACATGCTCCATCCTGCCAATTCTC
CATCCACATCCTGTGAGACTACCAGAGTTGTCTGTTAAAGGAGGAATTTCTTCAAGACTTGAAATGCAGA
AGTCCAGCTCAACTGATAAATTGATAGCACTTATTGTTGTCTTGAAGTGGCTTTACGTACCTGAGACATC
TGAGCTGCAGTGTTTCCCTTTGCCCCCATGAAAACCATGGCCAAGGCTGATGATATGCTCATGGGGAAAA
AAATAAGTTGTTTGAGTTGTTTTCCCCTAGCTTTTTCAAAAGGTTTAATGCAAATGTGCCATTTGCTTCT
GATAGAGCATCCATGACGGTGAGCCTGAAACAATGGATTTTTAAACAATATTACATTAATATAGGCTTAC
ATGTGTATTTACTTTTCACTCTATTTATTACTAGTTAAATGGATACTTGTTTTCATTGAACAAATAGGTA
CACACACAAAAACTACACTAGGGCTTTTCTTACAAGATGTCATTTAATCCATACAAGCTGATGAGATAGG
TGCTGTGAGTGAATGTCTGCACTTTACAAGCAAAGAAATTGAGCCTTCACTGTTTAAGTCTGTTGTGCCT
GAGATCACTCAACTACAAACAGAAAAGTAGGCATTAGAAACCAGGTCTTTGTGGTTCCAGGGCTCCTCTT

FIGURE 3 (continued)

AATCACCATGGTATAAGGACTTATAACAAAAGCAGCAGCAGAAAGCAAGAAAGTTACTTGCTTAAAACAT
GAAATTTGTAAGAAGAAAAACTATTGATTTCCAATACTGGTAAAATAGGTATTCCCTCCTATATTCCATA
TGTGATTATGTAAATTGGGACACCAATATTTTCAGAATGTAACTTAGAATTATGTTTTTATAAATGGAGG
AAGGAACACAGGGATGGTGGAAGGGTAGGAAAAAGAAAATGCCATGAAAATATTTATACCTTTAGGATGA
AAAATTCCATTTCAAAGAATTTCACTAAAGATAAAGCTCACAAGTACTGATAAAAACAGTATGCAGAAAG
ATGACTACTGAAGCACTTTATATGCTACAGAGAAAATATTTAAATACCCAGCAACAGAGAACCAGTTAGA
TTCTGTCAAATCCATGATTGAATATAAATGGAGATATTAAAAATTACAGTCATGCCATGAGAAAATACAA
TATTAAGTATAAATTAAGAATAAAGTTACATGTAAGTATAATTCATAGATAAAAAGACTACAGGGAAACA
CTGAACATCACATATTTCTGGATAATGAGTAATTCTAATTTTATTTATATCCTTTGCTATTTTCCCTACA
ATGTGCCTATATTTGTTTCAGTGTCATTTGGTCATTGTGCTTTTATGAAATTAATGGACTTGCATGTAGT
TGAAAAGTGAGATAACACTAGGCGAGATCTTTTTTTTTTATTATTATACTTTAAGTTTTAGGGTACATGT
GCACATTGTGCAGGTTAGTTATGTATACATGTGCCATGCTGGTGCACTGCACCCACTAACTCGTCATCTA
GCATTAGGTATATCTCCCAATGCTATCCCTCCCCCCTCCCCCCACCCCACCACAGTCCCCAGAGTGTGAT
ATTCCCCTTCCTGTGTCCATGTGATCTCATTGTTCAATTCCCACCTATGAGTGAGAATATGCGGTGTTTG
GTTTTTTGTTCTTGCGATAGTTTACTGAGAATGATGATTTCCAATTTCATCCATGTCCCTACAAAGGACA
TGAACTCATCATTTTTTATGGCTGCATAGTATTCCATGGTGTTACACAAATCAACCAGTGTCTTCCCACT
ACTCCCAACTCCCCAGAAACAATCAAACCTCAGTGCACCCTTTCTCTTGGTATTTACTTTCATATTTAGA
AATAATTGTGTATATGACTATTTTTAACCCCACAATTTTTGACATTATAAATTGCCTTCCTAATTTAGGG
CTGATGATTAATTTTCTTTTATCACTTACCGTACTTCACTTCCTCTCTCCAAGTGTTTGCCTTATTGCAA
CTAAATAGTATTCGCTGCTAAGCCAATTAATCAATAATGGATGCATTGCTTTTTTTACACGTCTGTTTTT
CCTTATGTCACTATTGCCTTCCCCTCTTTTCTTGTTTTCACTTTTTAAAAATCTATGGCAAATTCCCCTC
CCACCAAATATTCTACAGATCACTCAAGCTCTTTCAGTAATTTCTTCGTATGCTCAACCACATATGAGTA
ATCTATCACTCCCATTTCTCATCTCCCACAGTTTCCCCCCTGCTGGTGAGTGCAGGTTTATTTAGTCTGT
AAGATTTTCATTCCCGAAGCAGAATTTTCATAAACAGAGACCAATTTTTTCTATTATTATACCTTATTTA
GTCAATGATCAATTAATTTCTTGTTAATTTGGTAAACAAATTGTTTTCCTTAAACTTTAAAGCACACTGC
TAACACAGCAAATACGTTATTTTAAACATTTAAGCATTGATGATAAAGCTTAATGTATCAGATGTTTTAA
AGATGTAATCACTTTAAAGAACAAACTTACAAAATTAACAACTATATCATTAATATAAGCATTTGTACAA
TAATAAACTGAATAAATCAACACTTATAAATCTGTTAAACTAGATTCTCCTAAGACTTTCAAACATGTTT
TAAAATACAACTGTACAACAGTGATTATAAAACTTATTTCTAGCACCCCACTAGTAATACTGTGGGTTTT
ATACACTTTATCTTCACTCTATCTTTTTATATTTCCTAGGGTGATGGTAATGCTTATTTTAATACTTTTC
TGGGGTTAAATTAATAACAGACCATCTCCTATTCACAAAAACAATAGGATGGGGCTGCCAGATTGATGGT
TGGGACATGGGCTCTGACTGACCTGACACTGCTACTTTTCAGGTCATACTGCTTTTTAAAGCCAAACAAA
TGTAAGGACCATTTTGCAGTTTGGTCCTACATTGGGATTTTGCAAAGACAACTATTAAATTTGCTTTTTT
CTTTTTTTTGCCAAATGCCTTTCCTTGAAATGAAATACTATTTGAGGTTCTCGTGCATCTGATTTGCGTA
ACACAGAGTTCTATCCACAAGTTGGCTTTCAAAGTCTCCTGGTTTAATATTTAGGCCTTCAGGTTGGTTT
TTGTAACCACTGTGCCTGTCAACCTAGGTGCCTATAGTCACTATTCCTACACAGCAGTCGTATATGAATC
ATCACACAGCATTTCTTGTAAACATTATTGAAATTATTTCCTGCCTCCTTTAAACTCATCTTACATTTTT
TTTTTTTTTTTTTTTTTTTTTGAGAGAGAGTCTCGCTTTGTCCCTCAGGCTGGAGTGCAGTGGTGCAAT
CTTGGCTCACTGCAACCTCTGCCTCCCAGGTTCAAGCGATTCTTCTGCCTCAGCCTCCTGAGTAGCTGGG
ACTACAGGCCCATGTCACGACACCCGGCTAATTTTTGTATTTTTAGTAGAGACTGGGTTTCACCATATTG
GCCAGGCTGGGTCTCGAACTCCTGACCTCGTGATCCGCCCCCCTCAGCCTCCCAAAGTGCTGGGATTACA
AGCGTGAGCCACCGCGCCTGGCCCATTTTACTTGTTTTATCTGAATTTACTAAAGGACTCTTTCTTGGCT
TTGTTGTAACATGTATTTCAATTAACACATACTGGTTTTTGTTCTTGAGCAAATTCTCACAACTTGTCTA
CTGGGAATCTCTGTAAATTGGTTACTTTCTTTTTACACTATCCCAACACTTTTGCTTTCTGGCAACAGTA
TCGTCCTCATTTTGATTTTTTTCCAGTCCAAAAACATACTATCAACGCCTCTCCTGGTTTCTTTTAAAGG
AGGAGGAATGTCAAGTACAAATTCTGAATACTGAGAGCATACGAGTTTCGGTACCGACAAATAAATACTG
CTGCTGTTGTTTTTCCTGGAGGTCCCAGGCCTCACAGCCCCTTCCAGCGCCCAACATAAACTTCACCAGG
GTGGGAGGCCTCATTGTACCTACTTCCAGCTCCTGCAGGATGAGTGGAGCCCAGGCAGGACTTTCACCCC
CCAGCTCCGCGCCCATTCGCCCTGGCCTCCCCTCCCCGCGCCTGGACCCATAGGGCACACAGCCAAGTGC
AGCCAAGTCCCTGCCCTTAGGGAGCCCCCGCCAGAGACCGAGTAAAGAAGGACAGCCCCAGGGAAAGGTC
TGGAGCAACAGGTGCGCTGAGCACTTCACTGGGCTTCCCTTTCGTAGGTTCCCGCCCTTTTCCTGGGCTC
AAGAGCAGGTAACGAGAATCCAGCGTGTGGGAACCACTCCCAAAGTCAAACACCTACCCCAGTTCTCCGC
GCAGCTGCCCAGGAGCGAAGTGAGACCGGGTCGGAGAGGCGGGAATAGAGATGTCTGAGCGGCGCCGGGT

FIGURE 3 (continued)

GTTAGTTCCCAGTGAATGGGGAGGCGGGCGGAGTCGGGCCCAGCCAGGCACCACCTAGCGGGCGCCTGGG
CAGGAGGGCGGGGCGGGTCCCGCAGGCCGCGGGGATCTCCTGATGTGCAGGAAGTGGCCAATCTCTGTGC
AGGAAAAAGCCCCAACTGTCCGGGAGTTTTCAGTCAAGAAGCGATAATGCGCTTTGGCTATTTGGGGTTT
TTCGTGGTTCCATACAAATTATAGGGTTTTTTTTTTTTCTATTTCTGTGAAGAATGACATTGGTATTTT
GACAGGGATTGCATTCAATCTGTAAATTGTTTGGGTAGCATTGTACTTTTAACATTAATTATTCCAACCT
ATGAGCATGAATATGTGTCCATTTTCTGTGTGTGTTCTTCACGTTTTTCTCATCAGTGTTTTATAGTTGT
CCTTGTAGAAGTCTTTCACTTTTTTAATTAAATTGATTACTAGGTATTTTATACATCATATTTCTTATAG
CTATTGTAAGTGGGATTTCTTTCTTGATTTCTTTTTCAGACTGTTCACTGTAGATGTATAGACATCTTAC
GGATATTTTATATCCATTTTGTATTCTGCAACTTTACTGATTCATTTATTAGTTCTAGTAGTTTTTGAGG
GGAGTCTTTTGGTTTTTCCGATTATAAGATTATACCATTGGTGAGCAAAGCTAATTTTACATCTTTCTTT
CCAGTTTGGGTGTCCTTTGTTTCTTTTTCTTGCCTAATTGCCCCGGCCAGGACTTCCAGTCAGATACTGA
ATAAAGGGGGTGAAACTGGGCATCCTTGTCTTGTTGCAGATCTTATAGGAAAGGTTTTCAATTTTTCCCT
GTTCAGTATGATATTAGCAGTGGGTTTTTCATTTTGGTTTTTATTGTTTTGAGGTATATTCCTTCTATAC
CCAATGTGTTAAGGATTTTTATCATAAAGAGATGTAGGATTTTACTGAATACATTTTCGGCATCTATTGA
AATGATCGTGCAGTTTTTGTTGTTGGTTCTTTTAATGCAATGTATCGCATTTATTGATTTGTGTATATTG
AATCATACTTGCATACCCGGGTGAATCTCACTTGATCGTGGTGAGTGATCTGTTTAATGTGTTGTTGAAT
TGGAGTTGCTAGCAATTTTTTGAGGATTTTTTCTGTTTTTTTACCTGTTGATATGACGGATTCCTTTGATT
TTCAAATGTTGAATTAGTCTTGTACACCTGCAATCAATCTTACTTAGTCACAATGTATAATCCAACTATT
TTACACATAGTTTGATTTCATTTGTGAATATGTTGTTCAGGATTTTGCATCTATACTAATGAAAGATATT
GGTCTTTAAGTTTCTTTTCTTCTAATGTCTTTGTCTGGTTTTGTTATCAGAGTAATTCCAGCCCTATAGA
ATGAATTAGAAAGTAGTTCTTCTGCTTCTATCTTCTGAAAGAGATTTAGAGAATTGGAGTAAACGTTTTC
TTAATTTGTTTTTAGAATTTACCAGTGAGCCCATCTGGGTCTGGTAATTATTTTAGATGGCTATTAATTA
TTGATTAATTTTTTTAGTAGATATAGGCCTATTCAAATGTTCTATTTCCTGTTGTGTGACTTTTGGCGGA
TTGTGTCTTTCAAGAAATTGATCCACGTCATGTAGTTTATCAAATTTGTGGGCACAGAGCTGTCCTGAGT
ATTCCTTTATGATTTTTTACTGTACATGGGATTTTTAGCATTTCACCACTTTCATTTCTGATATTAGTAA
TTTAGGCTTTTCTTTTTGCTTAGCCTGGGTACAGTCTCATCAATTCATTGGTCTTTTAAAAGAACTAGCT
TTTGTTTTCATTGATTTTCTCTCTGGATTTCATTCATTTCTGCCCCCATTTTTATTATTTATTTTGTTTT
GCTTAGTTGGGTTTAATTTACTCTTCTTTTTCTGATATTCTAAAGTAGAAGCTGTGGTGATTGATTTTAG
AGTTTTTAAAACAAAGTTTCTACTTTTTTAACGTATCCATTCAATGCCATGAATTTTTCTGGAGAGGTGA
CTCACATTGTCCAGTAAGCCAAGAAATGTTAAGTGTCTAAATAGTAAACTCTAACCTTGGGTGAGTAAAA
TATGTAAACTAGTGGATTAAATCATCTGTGATTGAATCCATTACTTAACTCACTACATTAGTTAAGCAAA
TATTTACCTTCACTCCTTCATCTTTAACCTCTTCACTTTTTTGAAGTCTTATCTCATAATTATACTCAAT
ATCTTATATATTTTTAAAAACACACTTTCTTTACTTTTGTATATGATTTTACTTACATAAATTTCAAGAA
AATGCAAACTGATCTATAGTGACATACGGTAGATCAATAGTTGCATGGAACATGGAACTGAGGAGAGGGC
AGAGAGAGGTGGGTGAGAGGCAGTATAAAGGAGAAGGGGATACTTTGGTGTGATGGATATGTTCACTATC
TAGTTTGTTTTTACAGGTGTGTACGTGTATATATACATATATCCAAATGTATCAGATTATATATTTTATT
TTTCATTAATTAATTTTTTATTACTGTTAATTATTATACTTTAAGTTCTGTGGTACATGTGCAGAACGTG
CAGGTTTGTTACGTAGGTATACACATGCCATGGTGGTTTACTGTACCCATCAATCTGCCATCTACATTAG
GTATTTCTCCTAATGCTACCCTCCCCTAGACCCCACCCCCATGACAGGCCCCAGTGTGTGATGTTCCCCT
CCCTGTGTCCATGTGTTCTCATTGTTCAACTCCCACTTATGAGTGAGAACATGCGGTGTTTGGTTTTCTG
TTCTTGTGTTAGTTTCCCGAGAAAGATGGTTTCCAGCTTCATCCATGTCCCTGCAAAGGACATGAACTGC
ATAGTATTCCATGGTGTATATGTGCCACATTTTCTTTATCCAGTCTATCATTGATGGGCATTTGAGTTGG
TTCCAAGTCTTTGCTATTGTGAACAGTGCCACAATAATCATACGTGTGCTTGTGTCTTTATAGTAGAATG
ATTTATAATCCTTTGGGTATATACCCAGTAATGGGATTGCTGGATCATATGGTATTTCTGGTTCCAGATC
CTTGAGAAATTACCACACCGTCTTCCACAATGGTTGAACTAATTTACACTCCCACCAACAGTGTAAAAGT
ATTCCTATTTCTCCACATCCTCTCTAGCACCTGTTGTTTCCTGACTTTTTAATGATCGTCATTCCAACTG
GCGTGAGATGGTATCTCATTGTGGTTTTGATTTGCATTTCTCTAATGACCAGCGATGATGAGCTTTTTTC
ATATGTTTGTCGGCCGCATAAATGTCTTCTTTTAAGAAGTGTCTGTTCATATCCTTCGCCCACTTTTTTT
ATGGTGTTGTTTGTTTTTTTCTTGTAAATTTGTTTAAGTTCTTCTTACAGTCTGGATATTAGCCCTTTGT
CAGATGGATAGATTGCCAAAATTTTTCTCCCATTCTGTAGGTTGCCTGTTCATTCTGATGATAGTTTCTT
TTGCTGTGCTGAAGCTGGATCCCATTTGTCAATTTTGGCTTTTGTTGCCATTGCTTTTGGTGTTTTATTC
ATGACGTCTTTGCCCATGCCTATGTCCTGAATGGTATTGCCTAGGTTTTCTTCTAGGATTTTCATGGTTT
TAGGTCTTACATTTAATACTTTATTACATCTTGAGTTAATTTTTGTATAAGATGTAAGGAAGGGGTCCAG

FIGURE 3 (continued)

TTGCGGTTTTCTGCATATGGCTAGCCAGTTTTCCCAACACCATTTATTAAATAGGGAATCCTTCCCCCAT
TGCTTGTTTTTGTCGGGTTTGTCAAAAATCAGATGGTTATAGATGTGTGGTGTTATTTCTGAGGCTTCTG
TTCTGTTCCATTGGTCTATATACCTGTTTTGGCACCAGTACCATGCTGTTTTGGTTACTGTAGTCTTGTA
GTATAGTTTGAGTCAGGTAGCGTAATGCCTCCAGCTTTGTTCTTTTTGCTTAGGATTCTCTTGGCTATGT
GGGGTCTTTTTTGGTTCCATATGAAATTTAAAGTAGTTTTTTTTTTCTAATTATGTGAAGAAAGTCGCTG
GTAGCTTGATAGGGGTAGCATTGAATCTATAAATTACTCTGGGCAGAATGGCCACTTTCACCATATTGAT
TCTTCCTATCCATAAGCATGGAATGTTTTTCCATTTGTTTGTGTCCTCTCTTATTTCCTTGAGCAGTGGT
TTGTAGTTCTCCTTGAAGAGGTCCTTCACATTCCTTGTAAGTTGTATTCCTAGGTATTTTATTCTCTTTA
TAGCAATTGTGAATGGGAGTTCACTCATGATTTGGCTCCCTGTTTGTCTATTATTGGTGTATAGGAATGC
TTGTGATTTTTGCACATTGATTTTGTATCCTGAGACTTTGCTGAAGTTGCTTATCAGCTTAAGGAGATTT
GGGGCTGAGACAATGGGGTTTTCTAAATATACAATCATGTCATCTGCAAACAGGGACAATTTGACTTCCT
CTCATCCTATTTGAATATGCTTTATTTCTTTCTCTTGCCTGATTGCCCTGGCCAGAACTTCCAATAATAT
GTTGAATAGGAGTGGTGAGAGAGGGCGTCTTTATCTTGTGCCGGTTTTCAAAGGGAATGCATCCAGCTTT
TGCCCATTCAGTATGATATTGGCTGTGGGTTTGTCATAAATAGCTCTTATTATTTTGAGATACATTCCAT
CAATACCTAGTTTATTGGGAGTCTTCATTTTTTATACCTTGGAAATAAAACTCTGCCTTTTCATTTTTCC
ATTCTCCATCAAGCTTCTTTATAAAAAGTGTATACACAGAGTGTTGTCTTTTTTTCACGTTTGATTCTCT
CCTGACCCCACTGCAGTTAGAAGTCCACCCCAACATTCTCTGAAATTCCTCCTGATAAGGTCACCACTCC
TTTTTTAACTGCCATGGCCAAAAGATATGCCCCAGGTCTTATCTCATTTTGTTTGTTGGCGACTTTTAGC
CCTTTCGTCTTCGGCCTTCCAAGGATGTCCAGAGCCCCCTTCCTTTCTTGCTCAACTCCTTTGCTTGGTA
TCCAGATTCCTTTCCTCCGATTCTAGGCCCTCTACTTTTCATTATAATATGATCTTGTCATGATCTTATC
ATATGACCTTAACTGTATCCATAGGTTCAAGTTTCAAATTTTACTTATTTCATCCATATCGCTAACCTGG
CTCTTGAGCTGTAGACGTTACCTGTGTACAACTGGACATCTCTCAGAAACCTGGGTGCATCCCTTCCCAG
TTCTCTTCACTAAATGATCAACAGCTCTGCCATTTCTATCACCTTCATGCTGCTTCAATCCGCTCTTTCT
CACCTTCATCACATCTCATTTCTCTCCTAAACAATTAATTTCCTTACAGTTCTCCTGATCAATGCCAACT
TATTCTCTCCTCTGAAGTCCATATAAACATTCCTGGACTTTTTTTGGTTGGTAGGCTGTTAATTATAGCC
TCAATTTCAGAGCCTGTTATTGGTCTATTCAGGGATTCGTCTTCTTCCTGGTTTAGTCTTGGGAGGGTGT
ATGTGTCCAGGAATGTATCCATTTCTTCTAGATTTTCTAGTTTATTTGCGTAGAGGTGTTTATAATATTC
TCTTATGGTGGTTTGTATTTCTGTGGGATCAGCGGTGATATCCCCTCTATCATTTTTTATTGCATCTATT
TGATTCTTCTCTCTTTTCTTCTTTATTTGTCTTGCTAGTGGACTATCAGTTTTGTTGATCTTTTCAAAAA
ACCAGCTCCTGGATTCATTTATTTTTTGAAGGGTTTTTTGTGTCTCTATTTCCTTCAGTTCTGCTCTGAT
CTTAGTTATTTCTTGCCTTCTGCTAGCTTTTGAATGTGTTTGCTCTTGCTTCTCTAGTTCTTTTAATTGT
GATTTTAGGGTGTCAATTTTAGATCTTTCCTGCTTTCTCTTGTGGGCATTTAGTGCTATAAATTTCCCTC
TACACACTGCTTTAAATGTGTGCCAGAGATTCTGGTATGTTGTGTCTTTGCTCTCATTGGTTTGAAAGAA
CCTATTTATTTCTGCTTTCATTTCATTATGCACCCAGATGTCATTCAGGAGCAGGTTGTTCTGTTTCCAT
GTAGTTGAGCAGTTTTGAGTGAGTTTCTTAATCCTGAGTTCTAGTTTGATTGCACTGTGGTCTGAGAGAC
AGTTTGTTATAATTTCCGTTCTTTTACATTTGCTGAGGAGTGCTTTATTTCCAACTATGTGGTCAATTTT
GGAATAATTGTGATGTGGTGCTGAGAAGAATGTATATTCTGTTGATTTGGGGTGGAGAGTTCTGTAGATG
TGTATTAGGTCTGCTTGGTGCAGAGCTGAGTTCAATTCCTGGATATCCTTGTTAACTTTCTGTCTCGTTG
ATCTGTCTAATATTGACAGTGGGGTGTTAAATCTCTCATTATTATTGTGTGGGAGTCTAAGTCTCTTTGT
AGGTCTCTAAGGACTTGCTTTATGAATCTGGTTGCTCCTGTATTGGGTGCATATATATTTAGGATAGGTA
GCTCCTCTTGTTGAATTGATCCCTTTACCATTATGTAATGGCCTTCTTTGTCTCTTCTGATCTTTGTTGG
TATAAAGTCTCTTTTATCAGAGACTAGGATTGCAACCCCTTCTTTTTTTGTTGTTTTGCATTTGCTTGGT
AGATCTTCCTCCATCCCTTTATTTTGAGCCTATGTGTGTCTCTGCACATGAGATGGCTCTTCTGAATATA
GCACACTGATGGGTCTTCACTCTTTATACAATTTGCTAGTCTGTGTCTTTTAATTGGAGCATTTAGCCCA
TTTACATTTAAGGTTAATACTGTTATGTGTTAATTTGATCCTGTCATTATAATATTAGCTGGTTATTTTG
CTCGTTAGTTGATGCAGTTCCTTCCTAGCATCGATGGTCTTTACAATTTGGCATGTTTTTGCAGTGGCTG
GTACTGGTTGTTCCTTTCCATGTTTAGTGCTTCCTTCAGGAGCTCTTGTAAGGCAGGCCTGGTGGTGACA
AAATCGCTCAGCATTTGCTTGTCTGTAAAGGATTTTATTTCTCCTGCACTTATGAAGCTTAGTTTGGCTG
GATATGAAATTCTGGGTTGAAAATTATTTTCTTTAAGAATGTTGACTATTGGCCCCTACTCTCTTCTGGC
TTGTAGAGTTTCTGCCAAGAGATCCACTGTTAGTCTGATGGGCTTCCCTTTGTGGGTAACCCAACCTTTC
TCTCTGGCTGCCCTTAACATGTTTTCCTTCATTTCTACTTTGGTGAATCTGACAATTATGTGTCTTGGAG
TTGCTCTTCTCGAGGAGTATATTTGTGGCATTCTCTGTATTTCCTGAATTTGATTGTTGGCCTGCCTTAC
TAGGTTGGGGAAGTTCTCCTGGATAATATCCTGCAGAGTGTTTTCCAACTTGGTTCCATTTTCCCTGTCA

FIGURE 3 (continued)

CTTTCAGGTACACCAATCAGATGTAGATTTGGTCTTTTCACATAGTCCTATATTTCTTGGAGGCTTTGTT
TGTTTTTTCTTACTGTTTTTTTTCTCTAAACTTCTCTTTTCGCTTCATTTCATTCATTCGATCTTCAATCA
CTTATACCCTTTCTTCCAGTTGATCAAATCAGCATGTCTCATGTGCATGTGTCATGTAGTTCTCGTGCCA
TGATTTTCAGCTCCATTAGGTCATTTAAGGTTTTCTCTACGCTGTTTATTCTAGTTAGCCATTCGTCTAA
TCTTTTTTCAAGGTTTTTAGCTTCTTTGCGATGGGTTTGAACATCCTCCTTTAGCTCGGAGAAGTTTGTT
ATTACCGATCATCTGAAGCCTTCTTCTCTCAACTTATCAAAGTCATTCTCCGTCCAGCTTTGTTCCCTTG
CTGGCGAGGAGCTGCATTCCTTTGGAGGAGGAGAGGCACTCTAATTTTTAGAATTTTCAGCTTTTCTGCT
CTGGTTTCTCCCTATCTTTGTGGTTTTAGCTACCTTTGGTCTTTGATGATGGTGACGTGCAGGTGGGGTT
TTGGTATAGATGTCCTTTCTCTTTGTTAGTTTTCCTTCTAACAGTGAAGACCCTCAGCTGCAGGTCTGTT
GGAGTTTGCTGGAGGTCCACTCCAGACCCTGTTTGCCTGGGTACCACCAGCAGAGGCTGCCAAACAGCAA
ATATTGCAGAATGGCAAATGCTGCTGCCTGATCTTGCCTCTGAAAGCTTTATCTCAGACGGGCACCAGGC
CGTATGAGGTGTCAGTTGGCCTCTACTGGGAGGTGCCTCCCAGTTAGGCTATTTGGGGGTCAGGAATCCA
CTTGAGGAGGCAGTCTGTCCGTTCTCAGATCTCAAACTCCGTGTTGGGAGAACCACTACTCTCTTCAAAG
CTGTCAGACAGGGATGTTTAAGTCTGCAGAAGTTTCTGCTGCCTTTGGTCATCTATGCCCTGCCCCTAGA
GGTGGAGTCTACAGAGACAGTCAGGGCTCCTTGAGCTGTGGTGGGCTCTTCCCAGTTTGAGCCTCCTGGT
GGCTTTGTTTACCTACTCAAGCCTCAGCAATGGCGGGCACCCCTCCCCCAGCCTCGCTACCACCTTGCAG
TTCGATTTCAGACTGCTGTGCTAGCAGCGAGCGAGCCTCCGTGGGCGTGGGACCCTCCCAGCCAGTCGCG
GGATATAATCTCCTAGTGTGCCATTTGCTAAGACCATTGGAAAAGTGCAGTATTAGGATGGGAGTGACCC
GATTTTCCAGGTGCCGTCTGTCACGGCTTCCCTTCGCTAGGAAAGGGAATTCCCTGACCAATTGCGCTTC
CCGGGTGAGGTGATGCCCCACCCTGCTTCAGCTTACACTCAGTGGGCTGCACCAACTGTCCTGCACCCAC
TGTCCAACAAGCCTCAGTGAGATAAACCCGGAACCTCAGTTGAAAATGCAGAAATCACCCATCTTCTGCG
TTGCTCACACTAGGAGCTGTAGACTGGAGCTGTTCCTATTGGACCATCTTGGAACCTGATCTCTCCTAAG
TTTTGTATTTTTAGTAGAGACAGGATTTCACCATGTTGGCCAGGATAGTCCCAGTCTCTTGACCTTATGA
TCCACCGGCCTCCGCCTCCCAAAGTGCTAGGATTACAGGCGTGAGCCACCACGCCCGGCCATATCTTCAA
ATATCTTAGTGGAGGGTCAAGCACTGAGGCTGGAACATATTTTTCCGGCACTCAGCAACCCGCGCCTCAG
CTTACAGACTGGTAACAACCAAGTGGTGAAGAAGATTCCTTATCTCTAGTGGCTTCCATTCCCTGAACTG
AAATAATAGATCTGGAATTGAAGAAAATTCACAGTCCATCAATATAAATGCAAATTGCTTTTTTCTCCCC
CTTACTGGAATTTCATGGAAAAATTCTGAATAAATTTACCTCTCTTGTTCCCACAGTTAAGAATCAAAAT
AATTCATTTTTGAGGGAAAAGGACTCAGCGATGCAATGAGGCCATGCTCTCCTGCTCCACTCTAGATTTC
TATTGTACTGTTTTAAAAAGAGAAAAAGTGATTGTATTTTTTAAACCACAGACCATCTTTTACATTTAGA
TGCTTAGATATTTTCTAAATCCTTCCCACATCAAATCTTTTCATCCCTTGAAATCCCTTCTTCACTAAAT
AACAGATTTGGGAAACAATATAAACAAACCATTTACTAGTTGTCCATAACTTCATTTATTAGACTTTTAT
TGTACTGAGCACTGCAACAGGCCATAAGGAAGTTAAGAAACAAAACTAAATAAAATATGTACCTTCTTTT
TCTCTGTATCTCAGATGAATGGGAAAGACAGGTTGTATTTACAATAGAGTGGACAGCGGCTTTAATGGAG
CAGGTACACAGCAGTATGAGAAGAGAATGATGGAAACAGTAGCTCTGGGGACTCGGGATGAATCCACAGT
AGCATCAGTTGAGCTGAGTCTTATAGGATGAGTGACTTTACAGATGGAGAGTGGAGAAAGAATATGTTAG
GCAGAGGGGACATATTTCTAAAATGTGGTTGTGAAAAGGTTTGTAGCAGGTGAAGAATGGGTATATTTTG
AGGGTGGAATAGAAGGTGTATACTGGGGAGTGGCACATGGTGACATTGAATGAGGTTAAACCCAGTCAGT
AGGTCAAGCCTAAACTGGGAAAGATTCTGTCTGCCATTCTAAGAAATTTGGGGCTTATTCTTTGAGCAAT
GGAAAACCATTATAGAATTAAAACCAGAGAAGTGGCATGATAGCATGATTTATTGATTTCTCTCTCTCTC
TCTCTCTCTCTCTCTCTGTCTGATTTACTTTAATGTCAATACTTAGGATGCAGGAGGAGACCAGAACACA
AGTATTTTGGGCCTAAGCCCAGACAGTAGCAATGCTGATGCCAAGAACTCATTAGAAGGCAGAAATCACA
GGAGCTAATGACCAAGTTGATTTTGGGGGAGAGGGCAAGGAAAAGAGCAGATTACTATATGACTTAGTTT
TTTAACATACATAATTGGATAAATGATGACCTTATTAACAGAGAGAGAGAACATGGGGGAAAGGAGTAGC
AAGTAAAAATGCCTGGAGACAGAAGTAAAGACTAAGGTATGGTGTAGAGGCACCAAGTGAAGTTTCAGGA
GACACAAATTGGCCCAGGCAGCTTGCATATAAATAAGACATTGGTCTGATGAAAGAAGCCTAGATGATGA
TGCCAATATTTATTTATTTAGAGATAAGGTCTTTACTCTGTCTTCCAGGCTGGAGTGCAGTGGCACAATC
ATGGCTCACTGCAGCTTTGGCCTCCTAGGCCTAAGTGATCCTCCCTCAGCCTCCCAAGTAGCTGGGATCA
CAGACATGCACCACCATGCCCGGCTAATTTTTTTTTCTCTTTTGTAGAAACAGGGTCTCACTATGTTGCC
CAGGCTGATCTCGAACTCCTGAGCTCAAGTGACCCTCTCACCTTTGCCTCCCAAAGCGCTGTGATTACAG
AAATGAGCCACCATGCCCAGCAATGCCAACATTTAAGATATGGCTTCAGAAAGAGGACATAGCAAAAAGG
ATGTAAAAAAGGAGAAGATACAGAAAAAGCTGGACAAAGAAAAAGAAGGAGGTGAATAGTATCAGCAGCT
GCTACTAGAGGAAAAGGAACATTAAGATTGAAGAGAGCCCACTTCTCAGTATTCTAGTCACTACTTACCT

FIGURE 3 (continued)

TAGTGAGAGTGGTTGGGATAAAAATCAAATTGAATTGGATTGAGATATAAAAGGGAAAAGTGAAGACAGC
CCTCTTCGACTACTCTTTCAAGAAACCTAGCCATGAGGAACTAGAGAGAGCATGCTGTCTACAGATAGAG
GGAAGCTGGAACAAGGATAGTATGGTAAGGACAGATGGCATTTACCATGTCTTTTGCCTTCTGAATAGTG
ACAATCAGAAACAGCAGGTAAAATACTAGGAAATTAGGGAAATGTCTTTGATTTAATGAAAAACCTAAAC
TAAAAAATGTATGGAAGAGCTGTTTAAAAAGGAGGATGGACAGGACCTGGGGATTGTTGGGTAGGAGGGT
GAGGAAGGAGAAAGCTGGCATGATTTGCAGACTTACTGACTTGGACAAGCCAGTGAATGGCAGTGACAAT
AAGCAAGATTGGGGAAAGAGGAAACTGAATGAATTTGGAAGAGAAAATGAATTTCGTTTTTGACATGCTA
AGGTTATATGGAAAGTTCAGGGGAAGTTTGGGAGGCAAAGGTGGGAAGGTCACTTGAGCTCAGGAGTTCG
AGACCAGCCTGGGCAACATAATGAGACCCTTTCTCTACAAAAAAAGAAAAACTTAGTGGTCCTCAACAAA
TCGATATAGTTGAAGTCACGGGAATGGAGTGATTTTCCAGAGGGTGTGTGAAGAGCACCAGAGCCCTAAG
AACGCCAAAATATAAGCGGTCAATAGAGGAAAAAAGAGCCGGAAAAAGACACTTGGAGAGGCAAGAGAGG
CACAGAAAGAACTAGATAAGAGAGTTACTGAAAACAACAAATAAAAGGAGGAGGACTTTTGAGGAGGAAG
TTGAGCAGTTTGGGGAGATGACCAGGTTCATATGGGATCACAGAGTGCGTGGCCATAGTTAAGTGGCAGT
AAAAGTGCCTAGATTCGAGCGGGTGTAGAATCTTGTGGGTTGGGGGTTAGCCGGGCATCTAGGAGGAACT
GAAAGCTGCAGATGTGTGGACAGATGATGGTGCAGGTACCGATGACCAGGAAGCTGAGCCAGATGCTGAA
ATCCGGAGATGTCGGGAAAAGAGCAGAGGCTCCCGTGTGGTCTAGGAGCTGAGTCAGACGGAGAAATACA
GGGCTCGGAGTCCCTGAAAGCAACAGGTAACTTCAGGCCCTAAAATTGGGGTAGCCCCGGCCTCGAGGTG
ATCCCTGCCCGAGCCTAGCGCCGGTTCTGGGCCAGGGCGCGTGGGGTGTAGGAGCGATGGGCGATGCTAC
CCGTAGCTCCGTGGAGAGATGGGGCCGGTGAGGCATCCCTAGGGCCACCCCCCCCAACTCCGGGGGGAGT
TCCTTCCTCCGGGCTCTGAGCACCAGCTGATGGCGCCCTCCTGAGCCCCTGCCTCCCCACACCGTGTTCT
TCCCTTCCGCGCTGGCCTTGCGGGAACTCGCCCGCCCCTGCTAGGGCTCCGCCCCACGGGCGGGCGTGGG
TTTCACTCGGAAGCTCTTTCAAGGATTCTGCGCCGCTTGCATTCTGCGGGGCTGGACTGTGTCCGCGGAA
GCTCCCCCATCCCCTCAGCCAACCCCGTGCTCCCCTCGAGGGCTCCTGGGAGGACTGGGCTGGCAGCGGG
GGTGGGGGTCGCAGGATGCCACGGGTAGGAGGTCATGGGGGGAGGATCACCTTGATGTCCACTTCGGGGA
GAGAAGGGTCAAGGGACACCTCATACACCCTAAGGAGACCATCTATTAGTTCCCGCCATAGCGCCCCGTT
TATTTCCGTCACCTCACCGATCACCAGCTGTAATTAGAATTAGGTGTTGTTGAGGCTGTGGTTCGCTCTC
CACGTCCACTAGAATTAGTCACCAGGAGGTGGCAGCCGAGGCACACCGCGTTCCCCCGCCCTGGACCAGT
GTTAGAGGCGACGCGCTCAGGCCTTCTGTGCGGACCCGGAAGGAAGGTCAGGTCCCGGGGCCCGAAAGGA
AGAGGCAGCAGCCGAGGATGGGCGCCCAGGAGGAGGAACGCGCGCTGCATTGCGCTCGCCGGGGCTAAGG
CTACTGGGGGATGTTGGTATTGAGTATTTCAGCCATCCATAATGACTATTTTTAATAAAACTTTTATTTT
GGAATAATTTTAGATTGGCAGAAGAGGTGCAGAGATAATACAGCTAATTCTCATATACTCCAGTACAGTT
TCCCCAAGTGATAACATCTTACATGACCACGGTACATTTGTCAAAACTAGGGCACCAACATTGAGAGATT
GCTACTAGCTAAACTTCAAATTTCATTTGGATTTCACTAGTTTTTTTAAGCTAATGTCAATATAAGTATTT
TTTAAATAGCAGAAAAAGGGGGTTTAGTTTTACAATCATAATTTATGAGCCACCAAAATGATTTTTTTGA
GACAGGGTCTTGCTCTGTTGCCCAGGTTGGAGTGCACTGGTGTGATCTTGGCTCACTGCAGTCTCAACCT
CCTGGGCTCAAGCAATCCTCCTACCTCAGCCTCCTGAGTAGCTGGGAACACAGGTGTGCACCACCATGCC
GGGCTAAATTTTTGATCAAAACGATATTCTTGAGAAACTTCGTATTTATCAATATCATATCACCTTTATA
AAGATTTTTTTTCATTTAATGATGTATATGAAATATATGATAACAAGTATCATGGATATTGCAAGTGATC
AAGAATTGTAAGGCATTCAGTTGAATAGCATAGTACTTCTGAAATGTAAATGAAAGTCACATTAGACAAA
ATGTTAACGTGTTAAAAATAAAAATCGTCATTCTCTCCAGCTGTACAGATATGACAGGATCATTAGAATG
CATTATTTCAAGATCTATTTACTTATATTCAAATGTGAAAAAGGTTTAGACTACAAACTCATTTTTGTGA
AAATTGTGCTTTTCCATCTCATGGTACATTTTTCACACTGTAAGATGGTCTTGTTTGTTGAGAGATATGC
AGGATTTAGGGGGAGCATAATCTTCCATAAAAAAAGAATGGTGTTGGTTTTATTGTGCCTGATGAAGAAGA
GGAATGGGTGATTTGCATTGAATTCAATGGATGGGACTCTAATTCGTATATCTATCTCACTCCCACTGCC
AGCTGCAGCTTCAGTACCTTGTTCATTTATTTCCACAAAAGCCTTATGGAAAACATTGGACAAAAATAGG
TTTCTTGCTGAAGACATTCCTGAGAAATCAGCTTTGCTTTGGCTGAAGGCATCACTCATCCCCATACTGC
TCAGGGTTGACTTGAGATCATAACTGTCTTCCAGCTTGAACTTGGGAAGGTGTAGCTGCACTTCATACAA
CTCCATCATGTCTGCACTGGTCCACTCATTCAGCTTCTCATAGGTGATGGCCTTTTCCAGCTGCCCATTT
GGAACCAAGAAAGAAAGAATCAGTAATTCCAAAGTGGAATGAAAAACAGTAGTAGAGAGAGCACCCTAGG
AATTACATAGGTGAATTATGATCACTCCCGTTACTCAGGGTGACAACACACACACATCTGGAAATCCTTT
GGTTGTATAATGTTGACCTTCAAAATCTTTTTTCTGCAGATTAATTGCTATCCGGATATAGGAGAATTAG
AGTTTAATTCAAAATGGAAGTACTTCTGCTATAGTATGCAAGACATCAGCTATACACTCAAATACATAAA
TATAAATATACATTTAGATGTTAGCTATACAAAAGCATATACTCTAGTTCAAGTTGTAAGCCAAGGCACA

FIGURE 3 (continued)

AAAAATCTTGTTTATCGACATGGGAGACAGCTCTTTGAAAACAAAATTTGGAATAAAATAACACGTCTAT
ACTCTAATCAAAACAACGTGAGATTAATAATTATAGACTAAGTCAAAAAAGAAAGAAAAGATAAGAAAAT
CCTCCAAATCTCAAAAGTAATTATTTTACAGTGAGTTTAAGGATGCTTTCCCTCTTCTTTATATTTTAAA
TTTTTAAAATGATAAATATGTGTGTACATACTATATATGTATGTATATATGTATACACAAAAATACACAT
GTATATATGTGTATGTTTGATTTTTTAAATGACATGTTTGTTTCAATGCACATGCATCTTCTAGACGGAA
GTTTTGGCTGTCAATGGCATACCTGTAAACCACTTACATTAATAACATGACAGTATCTTCAGCTCAGGAA
ATTGCACTTCTAGGTTTTTATCTTACAAGGGCTTGACTCTGATGGTTATTTGTCCACACTGGTTTTATTT
TCACTATCCTCTCCAGTTTCACAAATTTTATGACATAATTTGGAAATATTTTCTACATACTAGTAGGATC
GTGGAAACTTATAAGTATTAAGAGTCTGACACATGTGAAAAATTAGACACTGTGCAAAGAAAGACAGGCC
ATCCGTTGCATGAGACTCATGTTCAGTTTAGGCATGCAAATTGCTCAGAAGCATGGTTTGACAAAAGTTG
TGTCCAGATTAATAGAAATTTAGCTGGTAAACAGCTTAAATAATTCTTGAAGACAGTATTGATAGAGACT
TTTTCTCCTGAAGGTTGCTTACTTGATAAAAATGTTCAACAAATAAGTTTTGGAAGACAGCTTGATGTCT
GCGTACGTGTGTGTATACTAATGCAAATGGTTAAAATATTAATTTCAAATTACATAGGTCCTACCAGAGG
GAAACCTAGACTGATTGAAAGATGGTTATGATCAATCCACACAGTTCTGTGACTGACAAGGTATATTTGT
ATCTGTTGTACATGTGGCTATGTGTGTGATGACCCCAGGCTGGAGCTGTCTATACATTGCCTAACCTTTC
TGAGGAACAGTAATATTAATTTTATAGAGTGTTGTAAAGTTTAAATAATATTGTGAAGGTGAAGTGCCTA
GAACTCAAGGTACATTGGTGACCTTTCTCTATAGGAATTAAATAATAGGGAGAACATTCTTCCTGAGGAC
AATTGGGAGAAACCTTGGCCAAGCAGTTCTTTTCTTAGTAAACACTGGAAACACCCTCACATCAGACACA
CTGATGTTATTTACCTGTTCCAGCCCATTAATGTCTTCTGGCAGTAGTATAAGCAGGCTGAGGTCACGGC
TTTTGTAGTAGAGTTGAAGGCCCACTGCTTTTGGCTTTTCTATGTGAAAAATGTGAAGCTTTTTCTTCAT
AAACATCATTTGCACTGGTTTGCTTGTAGTCTAAAAAAAACAAAAAAACAAAAAAACAGGTAACAAGGTC
ATTGAAGAAGTATTCCACCAACTCCTTAATTCTCTACCATCATTGGCTCTCAGTTGGTGAAACTGCTGAT
TCTCTGCTAAATGCTGAATAAAGTTATCCAGACCTTCCTTTATGGAAATATCTGTTCCACTGAAAAGTAT
CAGCAATAGCAGATATGTGAGTTTCTGTTTCTAACACAACTGTGGTAACCTCTATAAATCACAGCAACAT
GTATTAAATCAAACTCTTAATATATGATCTTGTGTAAATTATGGAAATGCCAATAATCCAAAAACTAAGG
CATATTTTACATGAAAATATTTGAGAAAGTATTTTAGTATTATAAAAATTGACATTCACTAAGAGAATGC
AAAGACAAGCAATAGATGAGCAGAAAATATTTGCAAAACATATGAGACAATAATAAAAACTCAACAAATA
ATAAAAAACTCAACAATAATAAAACAAACAAGCCAGTTTTTTTAAATGGGCAAAAGATCTAAGAAACACC
TCACAAAGAAGACATACAGCACATGAAAAATGCTCAATCATATGTCACTAGGAGATTGCAAATTACACAC
GGCTACTAGAATGGCTAAAATATGAAACACCAAATGCTGATGACGATATGAAGCAACAGGCACTGTCATT
TACTGCTGGTGGGAACGCACAGTGGCACAGCCACTTTGGAAAACAGTTGGGCAGTTTCTTACTAAGTTAA
CCTAGTCTTACCATACGATGCAGCAATTTTGTTCCTAGGTATTTACTCAAATGTGTTAAAAACAGTGTCC
ACAGAAAAACTTGCACACAGTGTAGTATTTATAGAAAATTTATTTATTATTGCCAAAAAATTGGAAGGAA
CTAAGATGTGCTTCAATAGGTGAATGGATAACAAACTGTGGTACAATTGTACCCTAAAATATTATTCAGC
AATAAAACAAAAAGATCTATGAAGCCCTGAAAAGACATGGAGGAACATTAAATTCATAGTGAATGGAGCC
AGCCTCAAAAGGCTACGTGCTGTATGATTACAACTATGTGACATTCCAGAAAAGCCAAAACTGTACAAAC
AAAAAAAGATCAGTGGCTGTCAGGAATTTAGGGGGAATGGATGAACAGGTGAAGCACAGGGCACTTTTAG
GGCAGTGAAACTATTCGGAATGCCATTGTAATGGTGGCTACGTGATATTGAACATTTTCAAAATCCATAG
AACAGTACGACATCAAGAGTGGACCCAAATGTAAACTATAGATTTTAGTTAATAATGATGTATCAATATT
AGATCATCAATTATAACAAATATGCCACACTAATGTAAGATGTTAATAATAAGGGAAACTGTGTGTGTGT
TGAAGGGGGGACATATGAGAGCCCTATACTTCGTGCACAATTTTTTCTGTAAACCTAAAAATGCTCTAAA
AATCAAGCTTATTTTAAAATAAGACCAATTGCCAAATGAAAGCAAAACAAACACCCCTGCAACTTAGATG
TTGTAGACATATGTTACTTTTCCATTCTATGTCGAACTGTCCATCACAAAGCCCCACCGTATGCTAAGGT
GGTGGCCATACGACAAGGGCTGTTTACTGCGAGTACTCTAGCATACTGTGGTTGTTTCCAGAGAGAGCCC
ATGAATGGCCCCAACCAGAGCCCTCCTAGAACTAATGGCAAACACTTTCTCTGTCTACTAGAGTTGTGAA
GCTTGAAGACTGAATATGAGGCAACCATATTCCCTGATCATTATTAGAGAATGAGAGTAGCAACTAGAGA
GAAAAAGAGAAAGAGACAGCATGAGAATGAACTGGGATTATGTGTTGAGACTCTAAATACCCCAATCACT
CACTCCTGGACTTCCCAGTTTTTTGTCACCTCAGCTAATTCCAATACAATTCCCATTTTGCCAGAGCTAG
TTTGGAATACTTTTCTATCACTTGCAACTGAAAATTTCCAGTGAATATATAAACCCAGGTAACTATCCAG
CTCACTTCTCGTTAACCTACTCGATTATGTGTTCAGTTTCTTCCCCATCCTCACCCCACTGATTGAGAAA
TACCTATTGCACACATTCATTACAGCCATAGTTCCACAGCAGCACTGTTTGTGGCCTATCCCTAGACTAA
ACAACTGTAACAAACCTTGGTCAACTAGTTCCTTTCCTAGGAATTTGGAATGGGATTTTCCAACTGGTCT
CTAGAATGGCGAAGGTCCTGTGAGTAGCTATGTTCTGTCATTGTGAACTGGGAAGCAGAGAAAGTTAGAC

FIGURE 3 (continued)

CACAACCTGAGAGAAGAATGATGGTAGAAACAGAGTTGAAAAAATAGAGGAAAAAATCCTGACAACATTT
AAGTCCTTGTTTCCAATCAGGTCCCAAGGCCCAGCCACACTCCAGCCCATTCACGAGAGTCAAATCTATA
ACCTTACTTTAGTCTCCGTTTTTATTGCTTTTACTTATGTAAGGGTAAGAATTTGGTAGAAGTTAGTACT
GGTTTAGCAGGGCAGGTACAGAACTTGCAGTGAGGACTCTTAGGTTCTTGTTCTGGACTGCTTCTAACTC
AGGCATGCCTCCAGTCACTTGGCCACACTATATTTCTCACCTAGGAAATAAATATGAAAACTACCCTACC
CAGCTCACATGGGTGGCAAGGACTGAGTGATTGTATATTCAGAGAAAAACAAGGACAGGGGAATTTCAAT
GAATTCCCCATGGAACTGAAGGCTTTTAGCCCAGCCATCACTTCCCTGGTAAGAGCCATAGTTCACTAGA
ACATACAATCTAAAAGAAGAGTGAATTTATAAGAGAATCACTTGTACAATGCCATGTGAAAATCCAAACT
GATCTTTAAAAATTTCCTACCTCGTTTATTCTAAAAGGCTTTTCTGTGGTGTTTTGCACTAAGAATTGAT
GTTCCCAGATTCCTTTAAAGTATAGGGCGTTCACCAGAATCATCCTGGTTGTGGAATCCACAGAGTCATC
AGGCAGGAGATTCTGGATTTTACCTGTAAGAACAAAAGGCAGGTTGCAAATGACTTGTAGAAATATGTAT
ATTTTAACTAAAGACAACCAGGCTTCTATTTTTTCTGGAACTATAAAAGTTTTCTTTAAAAGTCCTGGTT
TTTGATTTTCTGGAAATGGACAAGTACTATTCCTGTCCAGAATAGCTGCTGTGAATAAATAGAGAAACCC
TGAAGAAATAATATGCTGGACTGTCAGTAAGCATTATTCCACATAAAGTACAAATTTGCATTTTAATTAT
AAAAACTTCCCCTGTAATATAAGTTGATTTGTAACCCTATTTCTTTTTTTTTTTCTTTTTTTTTTTTTTT
TTTTTTGCACTTTAGCTAAAGATTTTTTATTTCCAGAAAATTACAACTACTTGACTAACAACTCTTTGCA
CCTACTGATTTAGGTTGGACAACTTGTGAAACATAGTGGTAAAAAAGGAAGTTACTTCTCTACTTCAAGG
TTTCCAAGTTTGTGGTAGAAATCTAAAGAACATTTCTCTTAGCACTACCTCTGGGCAAGACACTTGTGCT
AAAATGTCCTTCTTTTTCTCTGTACCTTTATGTCATTGTTAATATACTCTATTCATCATTTCCCCTCCTC
TACTCTTAGAGTATAAATCAAGATCTGTAAAATTGCTCAATAACAGGACTTAACTGCCCTGGAGGAAGAA
GGGATTTTTCTTTCCTTTTTGAAATTCAGAGGGGGAAATGGTGGCATTTAAACTCCTGCCAAAAATTTTA
AATTTCTAACAAAAAAATAAAATAAATACTCTTGAAAATTAATTCATATGAACCTTTATTTTCCTTCAAA
ATTTACTGGCTAAAATGATGGAAAAAATATATACATATATGGAGATTAAGAGAAGGTGGAAAGCTGTAAT
TAGATAGGGTTTGAGTTTTGGCATTTCGTATTTGTAGCTGTTGGAAAGACTTTCTGTAGGACTCTCTGGT
ATTTGGTATCCAAGAGATACTATGGTTCATATGTTCATCCATAATCATACTAAAAAGAGCCAAGTATTGT
CACAAAAGCAGGTTTAGCTGGGTTTCTCACCAAATTGATTTACATGTGAACATGGAAAGTTCACATAGGC
CACCGAAATTGAAATCTCCTTAAGCTGATAAGCAACTTCAGCAAAGTCTCAGGATACAAAATCAATGTAC
AAAAATCACAAGCATTCTTATACACCAACAACAGACAGAGAGCCAAATCATGAGTGAACTCCCATTCACA
ATTGCTTCAAAGAGAATAAAATACCTAGGAATCCAACTTACAAGGGATGTCAAGGACCTCTTCAAGGAGA
ACTACAAACCACTGCTCAAGGAAATAAAAGAGGATACAAACAAATGGAAGAACATTCCATGTTCATGGGT
AGGAAGAATCAATATCGTGAAAACGGCCATACTGCCCAAGGTCATTTACAGATTCAATGTACCCCTATTT
CGAGGGGACTGAAATACTTCCTTCTTTTTCACTTCTGTTTGTAGCCACAAACCGTGAGCTGCTCTGATTA
ACATCTGAAAGGCTGTGCCAATGTTTTCCTGTTGCCCAAAATATTGCTGTGTGCAATTGCTTCTATCAGA
TTGTTATAGTTACAACTTAAACTGATATTTGGCTATCAACCCCGAATACATTCTCTCCAAACTCTCTAAT
AAAGCACCTTGAACGATTTATAAAAATACGTCAAATATATATCTCTCGAATCAGGTATTATAGGTTTGCT
CTAGAGGCACATGTTTGATAACTGAGGTAGATAAAACTGGATTGAGAAGAACCTCTTGGCCAACCCAGCT
TCACTCTGCAACAGACACTACTCAGAATAAAGGGCTGATCTTTTAAACTGCCAAAATACAGACATGGGAA
AGCTGTTAAAATTATAAGAGACAGCTTGTGGCACTTAATTTAAAAAATAATTTTCCAGGAAAATATTAAT
AGAATCTCAAGAAATAGTAGAAAATCTGAAAAAAAAAATTAAACATGATTGAAATTGTACAACTCTCAAG
TGATTACCTCCCGTGGAAACAGCATCAACCCCAGACATGTAGACAGGTAAATTCTTTTCAACCTTCAAGT
AAATGATAAATCTCTACACTATTCACACAGTTTCAAAGCACAAAATAGAAAATTCTCTGATTACTTTTAT
CAAGCTGGCATATACCTAGTATAAAAATGACAAGAAAGCACAAAATTCCCATCCGTAAACCCATTTCTCT
TGTGAATATAAACAAATAAACCCTAAATTACATTTTAGTAAATAAATCTAATTAATATACATTAGGAATG
CAAGAAACATATATTAGGAAATCTATTAATGTAGCGTGTTGCTGATATGGCCTGAATATTTGTGTTCCTC
CAAAATTCATATGTTGGAACCTAATGTTCAGTGTGATAGAATTAACAGGTGGGGCCTTTGGGAAAGGATT
AGATCAGGAGGGCTCTGCCCTCATGAATAGGATTAGTGTCCTTATAAAGGGATTGAGGGAGCCTGTTTGC
CCCCTCCACTATGCGATGACAATGAGAAGGTGTCACTTTGGAATTATAGAGCAAGCCCTAGCCACACGCT
GAATCTCCTGGCACCTTGATTGCGGACTTCCCAGCTTCCAGAACTGTGAGCAATAAGTTTCTATTATTTA
TAAATTACCCAGTCTAAGATGTTTTGTTATAGCAGCTGTAATGGACTGAGACAATTGCTTTGATGACTGA
TAGGAGAAAAAAATCATAACATCATCTGCAAAAATACTTTTGATCTTCAACCTTCATTTCTAATTTTAAA
ATGATGACTTTGTAAATTAAAATGAAGAATACTTCTATAATATTAAAAATAATATTTTTCTTCAACAAAC
CCATAATAATGCTAACCCAGAAACATTAGTGGTATTTATGGCCTGCTATGACTACCGTTATTTAACATTT
TTCTCAAAATACTAAGTAAAGCAAAAAAAATTAGATGAGATATTATATAAAAGGAAGAGACAAAATTATT

FIGURE 3 (continued)

ATTTGCAAATAATAAGGAAAGCAAGGAGAATCAACTAAAAAACAATGAAAACTAATAAGAAGTTCTTTTA
GGTGCTGTTACACTATTACGCTAAAAATTATCTTCTTATCTTCTAACAATAAACAATTAGAAAATGATAT
AATTACATCCTAGTGATACACCACATTTATAATAATTATGCTTATAAAATATCGTTAAATGATAACATCT
TATATACACCACTGATCCAAACCAGGAAGTTAACATTAATAGAATATTATTGACAGGTCATATTTAAATT
TCATCAGTTGTTTTAATAAAGTCCTTTTTTTCTGGGTTAGAAATCAATACAAGACCTTGCATTGCATTTA
GTTGTAATTTCTTCTTATTCACCTTTAATCTGGAACAGTTTCTCACTCATTCATTGTCTTTCATGACCTT
GACACCTTTAAGAAAGACTTCCCATTTGTTTTGTAGAATTCTCCTGAATTCCCAGTTTAGGTTTGTCTGA
TGTTTAATCAAGATAATATTCAAGTTATGCATTTTTGTGAGAGTATCACCGTGGTGGGTTGAATTGTGTC
CCCCAAAAACACGTGTCCCACTTCTAACCCGTAGTACCTGTGAATGTGACCTTATTTAGAAATACAGTCT
CTGCAGATGAAATAAAGTTAAGATGATGTCATATTGGATTAAGATGAGACCCAATCCAATGACTAGTCTC
TCTGTAAGGAGGGGGGAATTTGGACATAGGCACACAGAGAGGAGAGTGCCATGAGAAGATGCAGAGACAA
AAGAGAGATACAGATAACAAGAGGAAGCCATGTACCAATGCAGGCAAAGATTGGAGTGATGTATCAACCA
GCAAATGAGTGCCAAGGATTGTCAACAACCACCAGAAGCTATGAGAAGCTCATGCAAGTTTCTTCTCTAG
AGCCTTCAGAGAGAGCACAGCCTTGCTGACAGCCTGATTTTGACACCTAGCCCCCAAAACTGTGAGAGAA
TACATTTTTGTTGTTTTTAACCACTCTGTTTACCTTAATGTGTTATGACAGCCCTAGGAAACTAATACAA
CCACCAAAGTCATGCTGTGTTCTTCTCAATGAATCATGTAAGGAAGTGCATGATGCCCATATGTCCTATT
ACTGGTGCTATTAATTTGAACACTGATTTTTCCAATGTAAAAGGACTGGCTGGTTTTTTTTATTTTTTGGT
ATCATGTGGGAAGATACTTTGAGAGCGTGTAATATACTGTTTCCCATCAGGCTTTTGTCCACTAATTTTA
GTATCCATTTATAATTCCTATCTAAAACAATTACTACTGTGGTTACTATTGCAGATGGTGGTTTTCTATT
TCCATCATTCTTCTGTATTCATTAACTAGAATTCTACTGTGAGAAAGAGCCTTCCCTTCTTCATTTATTT
GGATCTTCAATTATTTGTTTATATCAGTATAGACTCATGGGTATTTGCTTTATTCTATGGGTTATAATCC
ATTACTATCATTATTTATTTTGTTGCACAAATTGCTCCAGATTTTGCCATTGGAAGCCTCCCCTGTTGGC
TCCTGTGTCCTTCTGACATATTCCCAAGTATTTTGAGCATTTCCTTACATTCTGTCACCACAAAAAGTCC
TTATCTTGTACTTCGCTTGTCCCAGCTCTGTTACCACCATTTTGTCCAGGAGCTCTGCTTTCTTTTTTTG
AAAGAAGGAGTTTAGAAATCAAGATCTTGGTGTCAGATATGCTGATTACTATTGGGATGTCATTGCTTCC
AGATCCTCTCAGCAAATGGGGCTAGGAAATGTATGCATTATACACACATCTGTATCTATTTCTACATTTA
TCTATTGAATTATCTTTCTGCATATATATTGAAGACTAGAAGGTCATATTGATACTTTCACTTCCAATCT
AATAACACAGGGTTCATTGTAGCCTTTGTCTTTGCCTTATTTGTAATTTCTTTCCTGGCTCTCATGATTT
CCAATATATTTCCTTATTTGCTTAATCCTAGAACAAACATAAAGTAGTTTCAGGATTGCAAATCCATTCT
TCTATTAAAAACAAATTTAAAAACTAGGGTACAATATTTGTGTACTTTTTTTCAGCCTTAAAATATATAG
TCGAAGTATACTTACTTTTTTTAACCTTTGAATTTATAGTCAAAAATGCTGTTTTACAAGGTTACTTAAT
GTTTTAGACCATATGTTTGTTTAAAAGAATGTATCTGAAACAGTGCTACAAGCCAAGATGCCATTAAAGG
ACTGGAAAATTTGAAGAATCCCGAAAGAGAAAATACAGATGGATTAGACTGATAGAGGAAACCACAGCAT
ACACACACAAAAGGCATCACAGATGACTTCTTGGGAGGTTGGGGTGTTGCTCAGGGAGTTAGAAACTCAA
AGGCCATGCATTCATGGAGCTTGTTGGGGGCAGGGAACATCAATGAGATTAATGAAATAATTCCATTTAT
TGCAGTGGCTCCTAACTTTGACTGCAAATTAGAATCTCCTAAAGACTTAAAAATACTGATGCTTGAACCT
CACTCCAAGATATCTGAATTAGTTCATCTGGAGTTAGGCTTAGTAATCAGTAAATTCAACTTAATATGTT
GCCACGATTGAGAGTCACTGGTTTACAGAAATTGTGTTTATTGACTTTCTATACCTCCCTGGGTACCAGC
AATGGGCTACAAATACATTAGCTTACTGTCTAGAGTAATGAGTGAGGACACCGTATGTCACAGTGGAGTT
AGAACAGTGTTCCCAAGGTACTAGGAATTCCCAAGAAAAACTGGAAGCTTCCCATGCCCAGAAGGCAAGT
TATAAACACAGCACATCAATGTCAGCCCAACAGTGACCATAGACAAGTTATTGTGATCTGTATTATAAAC
TAAGACTGGTAAACTGGGGTTGCCAAACAAAAAGACACACAGAAAACCAAAAGGATTAAACAGGTAAGAA
AATCCACCCTATGAGAGAGAAGCACCAACATCAACATGCACTAACAGGAAGCAGAATTAATACAGCAAAA
AGACTTAACAATAAGCAAAATTTACATATTCAGATAAAGCTGACTGATCTCACTAATGAAAAAGAAATAA
CCAATAACCATAAGTCTTGAAGAGAAAAGAAATAATTGTCAAAGCAGAACATAAATAACTGTGGAAATAA
AACTCTTGAATAGATTGAATAGTTGAATGAACACGGCTGGAGCAAAATCATGAGCTGGAAAAGGATAACA
GAAGGGCAAAGCAATGAAAAGTAAATATAAATGGAAAATCAAAGCAGATAGGATAGATTGTGAAATTTCA
AATTTGTTTATTGGAAGTACTGAAGGCAAGAAGGGACAGAATGAAAAGAAGAAAATCATGAAATAAATAA
TATACACAATTTTGTTTACCTAAAGGCCTTTATATTTAGATTTAAAATAATTGCCAGCAAAGTTATAAAG
TAAATAAATAAAAATAAAAAGACCCCTGCCTAGAACATAATGTTGAAACCTCAGAACACCAAAAAAGAAA
GAAAAGTATTCTAAAATCTTCTGGGGAAGGTTCAGGGTGCAGGTTTGTTGTTTTTATTAATGATGCTGGA
TGCTACTATCTAAAGGAAAAATGAAGACCTTGGAGAAGACCTGTTGAAAGCTCAAGGAAAGAAGTATCTT
TGAGATGGTTCAGGTAGAACCTAGTCATGCCAAACACCCTAGCAACTTTCCCTTAAGGACATATGGAACT

FIGURE 3 (continued)

CTGCCTCGACAAAGTCTAAGTTCCTAAAGAACTAATTAATTCCTTATTTTATTTCATGTTGAATGCTTCC
AAATAGCAGATATTTGTGTCCAAAATAGAAAATACAGAAGGATTACAGCTTTCTCCCTCTCTAGACAATT
CTGCTTCTGAGGAATAGAGTGAGGAGGGTCAGCTGGAGGAATGAAATAATGGGATGTGGCAAACAAGGCT
CAGTAAAAGATTCGAACTGTGTCCACCATGAGCTTATTTTTTGGTGCCTCTCATTTGACCAGTGGTATGA
TAACAGAGAATTTTTTAAAGTGTGGATGTCCCATACTGTGGCCATATAGTACTATAATCTGCAGTCTGCC
CTTTCTTCCATAAAGTAAAAGATTATTTGCTCAGTTCTTCTTCAGAAATGAAACTTCTAGACTTATGCTG
TCTAATATGGTGGCCACTAGATTCATGTGGCTACTTAAATTTAAATTAATTGAAATGAAATAAGTTGAAA
ATTCAGTTCCTCAGTCACATTAGCCACATTTCAAATCACCTGTGTTCACATGGGAATAGAAGCTACTCCA
CTGGACAGTGCAGATTTATGGCACGTCTCCATCATCATAGGAAGATCTTCTGGACAGCTCTGTAATTCAG
ACACCTGGATTTTGTTATGTACCTTCAGTGCATCAGTCTAAGCTGGGGAAGCAAGGCAAGGACCAACCCC
TAAGAGCCATGCTTATGTGGCACCAGACAACAGCTGTCTTCTTGGCTCTAAAAGGCTTTGCTAGGATGCA
AAGCTAGCAGATTAGTTGCCCCAGCCTTCCAATCTGTAGGATCCCTACCTGATTTCCAAACAACATAACA
GTCACCAGGCTAGGAATCTAAAACATAACATTTTGCCCAACTCCAGCACCATTCTTACTCCTACTCCTGC
TATGTTGAATTTGTGTTTAGGTCATAACATACTTTTGCCTGTACAATCAAATGTGGTCTCACACAAGCTA
CAAAAGTGCAAGTACCTAGTAACTGCTAGCTAATCTATAATTCTAAACAAAACAAACTTATTTTCAGATG
AATGCAAATCAGGATGGAAGTTAAATATCATAGTCACTCTTGCTTCACCACGGCTTTTGAGTCATGGGCT
CAATGTAAAAGGAACTGAGCACTTAGGGCTGCCAATGTTATCAATTCATTCCAATAAACATTAATGTTCT
GAACAACTGCTATGAGCAGGCCTGTTATGTGTGATTTAAAGCTGAAGGCAGAGTTATCGCACATAGAGTC
CTTGAGTCTAGCAGGGGACATAGATGTATAAGCAGTTAGTTTTGATAACAGTGTGGTAAGTGTCAAAGTA
AAGGTTTGCATAAATGTCTGGGAGCAAAGAGGAGGATGTTTAGCCTGAATGAAGCCCTGAGAAGTTATTT
GGGGGCAAAGGAGGGGTTGGGGGTGGCAGGGCAGGGAACGGTATTTCAGATAGAAGAAATGGCATGAGTA
CAGGGCCATTAAGTAGCACAGGGAGTTCGGGACATTCTATGACATGTAGAATCCCTGAAATATAAATTTT
AATCCAGGGAGTGACAAGAGTTTAAGTGGAGAGACAAGCAAGGCTCCACAGTCATATTGGCCCTTATATG
TCTGGTTAAGGGCTTTGTGTTGATCCCATAGGTCATGGGGCAGCATGAATCAGTTTTGAGTAGAGAAGTG
ACATGGCCTATCTGGTCTAATTTGTATTCTAGGCAGGTAATTTGGGTGGTAAATGGAGGTTAGATTTGAA
GGGAACAAGATTAGAGGCAAATTATTGCATTTGTGCAGATAAAAGATAGCGAAGAAAGAAAGGCTGTGGA
GGAAAGGAATTGAAAGGAAAAGTGAACTCTGAGAAACATTTAAGAGGAAGCAAAGGAAAGGGTAGAATTT
AGAGTATGTCTCAGATTACTGTTCTGGGCAAGTGTGTGATTGGTGTACCCATTCACCAAGATGGAGAATA
CATGAGGAAGACAAGGTCTGGGAAAACCATTCTGAATGTGATTTCAGGTATGGTGAATTTGAAATGCATG
GGACCCTTGGCAAATATGTCTAGCAGGTGTTTGTTATGAGCCCTGAAGTTCAGAGGAGAAGACAGCAAAA
CATTCCATGTGCTTAGACACAAAGCAAAGGCATCATCATTAATATTCATTAATGACAAATGATGAATTAA
TCTTCATTAAGTCATGAATGATTAATTAATCTTCATTAATGATGATGCCTTTGTATTTCTTCATAAGATA
TAATATAATATCAATTGAAATGTTGATTTAAAAGGCAGCATGGTGTGTAGAAATCAGTTCAGACTTTGGA
ACTAAGCTGACTTATATTCGAAATCCTATTGCTGAAGCTTTAAACTGTGTAATCATAGATAATTTCTCTA
AAATCTCAGCTTCCTTATTTCTAAAATAAGGATAACAATAAAAGACTGTTAAATTGCCTGGGAGAATCCT
TCTACTACTTCCTTTTAGAAATAAAACCCTGAAATTTAGGTGACAAATGGCAACCCAGCTGAAAACTCCA
TTTTGCAGGTCTTTCTTCTAGCAAGTATGGTGACTGGAATTGACTGGAATGTGGTTGGTCACTCTTGCCT
GGAATTAGGGGCTTTTTGATCCTAAAACTAGGAAAGTCACAGGCAAACCAGAATGCACTGGTCACCCTAG
CAGAAAGTGTGCTATGGACTAAGTTTAGACCAGTGGGAGATGAGTGGAATTAACATGTGAAACTTCCAGG
GCATCCCCTTAAAGACAAATTAGCTTTTGCTGAAATTTCTTTTCCCCACTTCCTGCTGCTACTACAACTG
GCTATTGTAAGAACCATCTTGCACCTAGAGATGGAAGCCATGTATTGAGGATGGCAGTGCTGAACACCAG
CCTGGATCTCTGGATGGCCTTGGGAGGCAAAATGCTCTCTCTAAGCCAGGATGCCTAACTACCTTTGAAC
TATTATTTGAGAGAAAGACATACTTGTGTCTTATTAAGCCACTATATTTTGGGTCTCTTCTTTAGAGTAG
TTTAATCCATACTCTAACTGATACTTGAACTTACTTTGAAAAGTATTTAAGATTCTATAGCACATTTAAT
GCCACATTTCTGTTATTAGTAGATATTTTTCCTTAAAAACCATGCATGTGGCAGTATTTTCAATTTCCTT
TTTGCATTTTTCTGCTTTTTACCCTTGGGCTCTTCTTTGGAATTAGTGGGAGATGATAATTTTCTTGTCT
ATTTGGTAAAGTGATGGCCTGACTTACTTGTTTTAGATAAGACTTATTAGGAAGGCAGTGAATCTAAAAA
TTACGTACATGAATAGAAATAAATGTTCTGAATATTTACAATGTGTCCACACTTCTATTTAAGGAGTATA
CATACTTACATATGACACAAACTAAAATAAATACAAGGATGTTTGGGAAAAGCACGCTGCCAAACCCCTT
GGTGAAAGCTTACCCTCGGTCTGTCTTTCAACCCAAGAGTTGATGTCCTTTCTGATTTGATCAGAAGCTT
CCACAAAGTTAACAGGCTGAGGTTCTGCACCAAAATATGTTTTCATGTCTTCTAAATATTTCTGAAAGAC
ATAGATAAAAATCCCCTTTTGTAGAGTTTGTTCAAAATTGAGAAATCAAATCTATTTAGATTATCAAAAG
AACTAGGTAGGCGGGCAATTGCACACTCCCACACCATCACTCCATCCTCTCTTTCCTGACTCCCAGTTTT

FIGURE 3 (continued)

GGTCAAAAACTAAACACCTCACTCTTCAAACTTAGCAGGGCACTGGCTAGCTATGCAGAGCTCCAGCTGT
GGAAGGAAGTACGGATGCCCACATTTTTGGGGCTTCCACATCCTCTTCCTTTCTATTTTTATCCATGCCT
TGAAATGAGGCTAGAATGGAAAGGGACTACAAATAACAAGAGTGACCCCAGTGGCCAAGAGGTACTGGGC
ATTGTACTTGACTTTTTATGGTAGGTATGAAACCAAAGTGAGGCTTGTGATACTGGTAGCTTCCTTCTGT
GGATTCTAAACAACAAGAATCTTGTGGAGGACCCTTGAAGAAAATGATATCCTGCCATGAAAATGGATTT
CTAAGCAGAGTTGAATGTTATATTAGGCATTCTGAGGCAAAAAAAAAAAAAATGAGGCCTTCACCTCCTC
CTGGTCCTCTGATGTTCACCCAGTGGCAGTCATCACATGTAGGCTATGACTGAGTTTGCTGTTATGGAGG
CATCTGCCTTGGGAACACAATTTATTCTTCAAGACATTGTAGTATTCCTTCAATTTGCTTACTTTATGCA
GGGCTTGTAGGAGAAAAAGTGATGAGTTAATTCTGTTGCCAGGAAGTGGCTTGAAGATTATGAAGTCTAA
ATTCTGTGGAATTTAAAATCTAATAAAAGGAAAACTTAAATATTTTTGAGGGACCACTGCCTGTCTTAAT
TCAGGGCTTGTGGACATATAAAAATATGTTTGTCTCTATCTCTGTGTCCCTCTTGTTTCTAAGTGCCCAC
TGAGTCAATCATGTCTCCTACTTCTGCATCAAACGAGAGTCCATGAGCCTACAAGAAAGGAAACTGTCTT
TAAGATTCCATTTGGATGATTTTATGTCTTTAGTAATAACAAAGCTCAATTCCTGAACTCCCCAGAATTC
ACTAGATTTGAACAGAGATAGCATTGCTTGAAATCACAAGGTAGCTTTATTTTATCTTATTGCTATTCTT
CTACCCTATCTAATTTCCTTGCTCTTTGCCCACTGGACACACGGGTCCTCCTGCCCAAAGAGATGTTGGA
CAATGAAGGAAATTATTGACCTGGGTTGTCATGTGACCCTCTTAACAGAGGACAGAGTCATCATGGTCTG
CATTGGTGGGGTTTCAACCCTTAGTAAAGAGGAGAGGTTGATATTATTTCATGTTTCATGTTCCCAAAGT
CTGTAAAGTCTTGATGTGAAAACTCCTCACTTCTCTCATCCCAAGGTCAGTTTTGCTCTCAAGTAGACAG
TCTCCAGCCAAGTCTCCATATGTATTTGTAGGCCATTCTCAGGGGCTACCTCTTTATTCTAGACAGAAAT
ATCTGATTCCTAGATCTGATTTGAGACCTGTTATTGGTTTCCTTTACCACTAGACACTCATTGGTTGGTC
TAATTGATTGTTTGCAGGGAAGTACTGACCACATGAAGATTGTCCCTGGATCCCTAAAGAAATATACAGA
GTTTACTGATTGGTCTCACATTGCTCTTTCTTTTCCATTAGCTTAAAATAAGACATTTGCACTTACATTG
TGAAATGCATACGTTTTCTCTCCATATATCGCATTGGCTGTTTTAAGTAAGTAGTCATCGTTGGGCTTGA
GGATTTCTGAGATAAGTGTTTGGAAATCAGAGTGTATTTCTTCCGAGTTGCTCAAGTTGAATTCCTTTAA
AAGAGAAGGAACTAGTCAAATAAAATGTTGAACAAGAGTTACGTACATGTTAGCAAACTAAAGCTAAATA
AAATTATTTGGGGAATTGCAAACAAAAGTTGAAAATGTTCCTAAAGTGGATAAAAATGTTTTCTTTAGTG
TTAGTGCAAAAGAATGAAATGTTATTGAGGCCATAATTTTCTTCACATTTAGTTTGCAAAAGCAGGCAAG
GAAAAGTTTGAAACTAGAGAAATTTTTAGAGAGATTAAAAGGGCGTGGGGACAAGAGATCTTTCAAAAGG
TGTAGATATTTTGTATTCCAAAAAAAGTTTCTGTAACTTTAATATATGTTTCTAAGAAAAATTACCTGCT
AAAAGTTGCTTCAGTTATCACTAAAATACATGTGCTAAAAGTACTTTTTCCTTAATTATGAAATATATAT
TAAAGGATAAGATATACCATTTTCCTTTTTTTTTCACTTTCAGGGTCACATTTGACTCCCTGGTCTCTGT
TAAATTGAAGCACCTGTAATTTCAATAAAAATACAAATGAATAGACTGCAGAGAAGTAATTATATAAATC
ATACATCATCTGTAAATACAAGTCAGTCATTCCTATAATTGCAGAACATATAATTAGTTAAACAAAGGGG
CTCTGACTTGACTTAATGTGTGTAATAAAATAAGTCAAGAACTGCTCTTAAATAAATTTTCTAAAGTCGA
ATTTAAGTTGCTAGTCTCTTTATTTTCCTATGTTTTGTAACTAGAATGATGTTAGGAAAACCTTGAGGTA
AAATTCTCTTATTTTCCGTATTTCCTTTTTACTCATGGTTGTTTTAAGAAGAATGCTAGGTGTCCAACTG
AGACCATCATTTAGACAGTTTAGGTAAAAGCCATAATTATGTGGAAAATTAAGGAATTTTAGTTGTTTTT
TTTCTAGTTAAATGCTCAGTTCCTATTGTCTACCACCACTTGACATATTTAGGCGCAATGTTTGTGTTTA
CCCCAGCATTTCACTGGAAAGTTAACAGGAAAGATGTAGATACTCTTCTTTCCTTGGAATTGTACAACAA
TAGAACAGAAGGCAATACTTTTATCTGCCAAGTCCTGGACCCGGCTGACAATAAGAAATACGGTATACTG
CTTCAACGGTTGCATTGACCCATGTTAACAGAACAAGGGCCACCTGCCATACATAAAGGGGTGCACAGTT
AATTCATGAGGCCCATTTGCAACTAAAAGTGTTAACATCCGAAACAAGGACAAGCAACACCCAGCAATAT
ATTTATATGAAATAGATTCACATTGGAATCCACTTAAGATTGTCTATCACATTAATGATTAAGACTTTTG
AGCTAATGAACCTGTCATTAACAAGTTGTGAACAAGGATTTTGTTGTTGCTGTTGTTGTTTTTAAACCAC
CTGATATCTTGTGAACTACAAGAGTAAGGATGTTATCCCAAGTCCAGACTAATATAGCATGTGTTCTGCC
CACTTCCCTCAGAATTACCAACCGTGTTCATATCCATACTTTCTGAGGAAGTCACCTTCTTGGGTGAAAA
TTCTGTCATTTGGCCTTTTGGTTTTGCAAGATTTAGGGCCGAGTTTACTCCTTCTGTTTTTTTTTTTTTT
TATTTAAAATCACATTTATATATACATATTGTTGCATATATATATGTATTCATATATATTTTTACACACA
CATATGGCTATTTTGCTATCTATGACTACATATATATATTTACATACGCACAATGTTTTGAGGATGCTTA
TTGCAAAAATAGTTCTGTATATAATAGTATTATATTGTTATTGTAATGATCTTAATGGGCTCCTTAGATT
CATTCAGATAACCAGGGACTAAACAAAGAGAGAATCAAACAAAGCATGAGAAACAGAATTCTTTTATTTT
TCTTTTTTGTGTCTTCAAGAAAATCCTTATGTGATTATAAAGATGCTGAATAATTCTATTATTTAAAGTT
TGACCAATTACTTTTTGAAATAATATCATCAAAATAAAATTGGTTTTGGTGTTGAACAAAAATTGATAAC

FIGURE 3 (continued)

CTTATCCTTTCTCCATTTTATTTTGCTAAAGGACACAGGTTCTCAAATGGTTTTCCTAGCAACAGTTTGC
AAATTGATTCTCTTTACCAAGATTTGTTTTATGGTATAGAATGTTTTAATGTATGTCTTGTTTTAGAGAA
TGTTATTGTGAAATGTAAATTATTGAGTTGTCAAGAGAAAACTGAAGTTAAAAGGCAATGAAAGCACTTA
GCTTACAAGAAACAGAAGATAGTTGACCTTTTCCACTCACCTGGGCCATTTGGGCTGCAGTGGTACCTTT
GGCGCCCAAATACACTATGGTCAAGGAAGTTGAGATGCTCCAGGAAGAAAAGAAGATATTTTTACCCTGA
GCAGATTCAGCTAGCTTTTTGCTCAACTCCAGGGCAAACTGGTTGATTGATGTTGCTAGAGAGTCCATTG
AGGAAACCTAAGAAAAATAAAGCAAAAATTAGAGAGCATATTAATATTTATTTCCACTTCACCTTTGAAA
AAATATGTATTCATAGTTGCATACATATCCATATACATTGTCATATGAGCTGAATAGACTTTAGCAAAAT
TCTAGTCCAATAATAGTATTTTATATATTAAAACACTGAAGTTTAGAGAATTTACGGGAATTGCCTCAAA
TTTTAGTGCTAATGTGCATTAGAGAATAAATGGATGCTGGTCAGTTAAAAGCTGAGTCCCATAACATAGT
TTTTGCCACTCTCTTGACATTTTTCACACCACCAGTTTTGTTTCCATGTGTTTGTATCTAGTTTTTCCAA
CTCCAGCATAAGCTTATTGAGAGCAAAATATTCTTTTTATGCTGCTTCGTGCACCCAACAGCACCTAGCT
AAGGATTTTGCACAAAATGGGTGCTTGTAAATATTTATTACTCATTTACGATATTCACGGTTTGGGCTGT
AACTACCATTTTTAATTTATGCAAACATGGAATCATGCACAACTAATTGGAAAATGCTTGTAGAGAAATT
GAGAAGTTAAGACTGTTTGTCTTTATTCTCACTCATTTGAGACCCTCTGAAACTAGTCTTCTGGAACAAG
AGTACTCAGTTTTCCTCATCTTTTTTGATATTATACTCAACATCTAAATGTCATCTCTAATGGAAGCAAC
CAAACAGCTGGCCAGCCTACCACACCTGCATGTACCTGGCCTGAAAATGACAGGTGCCCCAATCCACAGC
AAATGTGCACCACCACCACTCCATCACAAACACTCACAGCTTGGACCACTGAGGCAACTGCAGACATTAT
TGATGAAGACTACAACTGAGGAAACTGCATGGATATTATGCTACCAAGTCCACCCTAAACCAAAGCCAAT
ATACCATACCCAAGCAATACCATAATATTTTAATTTAAAAGCCTTTTAAAACTAGGTTTCTATAGTTAAT
TCCATCTATTTTGATTTTATGGCAAAATAATTTCTCGAATAAGTTAAACGATTTAACCAAGTGCTAAGGG
AATCTGTTACTGCTAGACCAGCCTTACAAGAAATCCTTAAGGAAGTTTTAAAAATGGAAACAAAAGAATG
ATACCTGTTACTTAAGTACGTAGCACACACACTTTATAAAGCAACCACACAATAGAAACCACAAAGCAAC
CAGCTAATAACTTCGCAATAGGATCAACACCTCACATATCAATATTAACCTTGAATGTAAATGGGCTAAA
CACCATATTTAAAAAGCACAGAGTGGCAAGTTGGATTAAAAAACAAGACCCATTAATGTGCTGTCTTTAA
GAGACCCATTTCACATGTAATAACACCCATAGGCTTAAACTAAGTGGTTGGAGGAAGGGCTATCACACAA
ATTGAAAACAAAATAGAGCAGTGGGTGCTATTCTTATATCAGATACAACAGGCTTTAAGCCAACAAAAGT
AAAAAGTGACAAAGAAGGGTATTATATAATGGCAAAAGGTTCAATTCAACAAGAAGACTTAACTATACTA
AACGTATATGCACCCAACATTGGAGCACTCAGATTCATAAGACAAGTACTCTTCAACCTACAAAAAGACT
TAGACAGACACACAACAATAGTGGGGGACTTTAACACCCCATTGACAGCATTAGACAGATCATTGAGGGA
GAAAACTAACAAAGAAAAACTTGACCAATTGAACTTATTAATAAACATCTACAGAATACTCCAGCCATCA
ACCACAAAATATACATTCTTCTCATCTGCACGCGGAATATACTCCAAGATTGATTACATGCTCAGCCATA
AAGCAAGTCTCAACAAATTTTTAAAAACTGAAATTGTACCAACTATACTCTCAGACCACAGTGCAATAAA
AATAGAAATCAATGCCAAGAAGATTTCTCAAAACCACAGAATTACTTGGAAATTAAACAACGTGCTACTG
AATGACTTTTTGGTAAACAATGAAATTACCGCAGAAATCAACGTCTTTGAAATAGACACAGAGACATAAC
ATACCAAAGTCTCTAAGATGCAGCGAAAAGCAGTGTTAGGAGGAAAGTTTATAGCACTAAATGCCTACCT
TAAAAAGTTAGAAATATTTCATATTAACTATCGAACATCAGACCTAGACGAACTAGAGAAACAAGAACAA
ACTAATGCTAAAACTTCCAAAAGAAAAAAACATAAGTAAAATCAGCAAAACTGAATGAAATCGAGACCCA
AAAATCCATACAAAGAATCAACAAAACCAAAAGTTGGTTTTTTGAAAGTATAAACATGATTGATAGACTG
CAGGCTAGATTAACAAAGAAAAAAAGAGGAGATATAAATAAGCACAATCAGAAATAACAAAAGTGACATT
ACAACTGATCCTGGAGAAATACAAATGATCCTCAGAGACTACTATGACTACCTCTATGCACACAAACTAG
ATAATCTAGAGAAAATGAATAAATTCCTGAAAACACACAACCTCTCAAGATTAAATTAGGAAAATATTGA
GACCATGAACAGATCAATATCATGTTTCAAAATTGAATCAATTATAAAATCCTACCAACCAAAAAACGCC
CTGGAACAAGTAGATTCACAGCTGAATTCTACCAGATGTACAAAGACAAGCTGGCATCAATGCTGATGAA
ATAATTTCAAAAAATTAAAGAGGAGGGACTCCTCTCTAACTCATTCTACAAAGCCAGCATCATCCTGATA
CCAAAACCTGGAAAAAACACAATAGAAGAAGAAACCTATAGGCAAATATCTCTGATGAGCATAGATGCAA
AAATGCTCAATAAAATCCTAGCAAGCTGAATCCAGCAGCATATCAAAAAGTTAATTTACCACCATCAAGT
AGGCTTTGTTCCTGGAGTACTATATTGGTTCAACATACAGAAGTCAGTAAATGTGATTTACCACACAATT
AAAAACAAAAAACATCTGATCATCTCAATAGAGGTGGAGAAAGCTTTCAATAAAATCCAATATCCATTCA
TGATAAAAACCCTCAACAGACTAGGTGTTGAAGGAATATACCTCAAAATAATAAGAGCTATCTGTAACAA
ACCCACAGCCAATATCATACTGAATAGGCAAAAGCTGGAAGCATTCCCCTTGAGAACTGGAACAAGACAA
GAATGCCTACTCTTTACCACTCCTATTCAACATAGTACTAGAAGTCCTGGCCAGAGCAATGAGACAAGAG
AAAGACATAAAAGGCACCCAAATAGGAAAAGAAGAAGTCAAACTATCTCTCTTCATTGACTATATAATTC

FIGURE 3 (continued)

TATACTTACAAAACCCTAAAGACTCCACCAAAAGCCTCCTGGAACCGAAAAATGGCTTCAGTAAAGCTTC
AGAACACAAAATCGACGTACAAAAATCAGTACCATTTCTATATACCAATAACATTCAAACAGGGAGCCAA
CTCAAGACTACAATTCCATTTATGATAGCCAAAAAATAAAATAAAATAAAATACCCAGGAATACACCTGA
TGAAGAAATTGAAAGATCTCTACAAAGTGAGGTAAAAAAAAACACTGCTAAAAATCATAAATAATACAAA
CAAATGGAAAAACATTCCATGCTCATGGACAGGAAACATCAGTATTGTTAAAATGGCCATACTGCCGAAG
GCAAACCTCGGATGGAATGCTATTTCCATCAAACTACCAACGTCATTTTTCACAGAATTGGAAAAACTAT
TCTAAATTTCATATGGAACAAGAAAAGAGCCCCAATATCCAAAGCAACCCTAAGCAAAAAGAACAAACCT
GGAAGCATCACTTTACCCAACTTCAAACTACACTATAAGCCTGCAGTAACCAAAACAGCCTGGTGCTGGC
ACAAAAACAGACACATAGGCCAATGGAACAGAATAGAGAACTTAGAAATAAAGCTGCACACCTACAGACA
TCTAACCTTTACCAAAGTAAACAAAAACAAGCAATTGGGAAAGGACTCTATTCAATAAATGATGCTGGGA
TAGCTGGTTAACCATATCCAGAAAAATGAAAGTAGACCCTACTTTTCAACATGTACAAAAATTAACTAAA
GATAGACTAAAGACTTGAATGTAAGATCTCAGACTATCAGAATCCTAGAAAAAAAAAAAATCCAGGAAACG
CCATTCTGGATATCAGTGTTGGGGGAAGTATTCATGACTAAGTCTTCAAAAGCAATTGCAACAAAAAACA
AAGTGAGACCTAATTAAACTGAAGAGCTTCTGCACAGCAAAAGAAACTATCAACAGAGTAAACAGACAAC
TACAGAATGGAAGAAAATATTTGCAAACTATTCCACTGACAAAAGTTTAATATCCATTATGTACAAGGAA
CTTAATTCAACAAGCAAAAAACAACCCCATTAAAAAATGCCAAAGGACATGAACAGACACTTCTCAAAAG
AAGACATACAAGTGGGCAACAAACATGAAAAAATGCTCAACATCATTAATCATTAGAGAAATGCAAGTCC
AAACCATAATGAATACTACCTTGTATATGTCAGAATGGCTATTATTAAGAAGTCAAAAAACAAGAGATGC
TGATGACGCTGTGGAGAAAAGGGTACACTGTTGATGGAAATGTAAATTAGATCAGCTACTATGGAAAGCA
GATTGGAGATTTCCCAAGGAAGTTAGAACTACCCTTCAACCCAGCAATCCCATTACTGGGTATACATTCA
AAAGAAAATAAATCATTCTACCAAAGAGACACACACACACACACACACAAGTGTTCATCACAGCACTATT
CACAATAGCAAAGACATGAAATCAACCTAGGTGCCTATCAGTGTTGGATTGGATAAGGAATACCTGGTAC
ATACACACCATGGAATACTATGCAACCGAAAGAAGGAATTAAATCATGTCTCTTGCTGCAACATGGATGC
ACTAGAGGCTGTTATCCTAAGCAAATTATGACAGGAACAAAATACCACATGTTCTCATTTATAAGTGGGA
CATAAGCATTGGGTACTCATAGACTTAAAGATGGCAAAAATAGACACTGGGGACTACTAGAATGGGGAGG
CAGAGAATGGAGAAAAGATTGAAAAACTAACTATTGGGTACTATGCTCACTACCTAGGTGATGGACTCAA
TCAAACCTCAACCTCAGCATCACACATTATACCCTTCTAACAAACCTGCATATGTACCCTCTGAGTCAAA
AGTAAAAACTGAAATTATTTAAAAAATAAAATAATTCAAATTCTTATACCTAGGAAATCTCATTAATGCC
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FIGURE 4

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FIGURE 5

Characteristic	Cases	Controls
	N=352	N=418
Gender (% male)	246 (70%)	182 (44%)
NIDDM (%)	36 (10%)	10 (2%)
Hypertension (%)	154 (44%)	53 (13%)
BMI (kg/m^2); mean ± SD	29.4± 5.7	26.8± 6.2
(range)	(16-61)	(15-58)
Current age; mean ± SD	48.1± 7.3	43.0± 14.3
(range)	(29-74)	(20-70)
Age at diagnosis; mean ± SD	39.3± 4.9	N/A
(range)	(22-51)	
Qualifying event		
Angiography	54 (15%)	N/A
CABG	53 (15%)	
MI	190 (54%)	
PTCA	42 (12%)	
Other	13 (4%)	

All variables differed significantly (P<.0001) between cases and controls

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<130> MMI-001PC

<150> US 10/017,128
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<150> US 60/327,488
<151> 2001-10-05

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Phe Leu Arg Glu Arg Leu Thr Asp Leu Glu Gln Arg Ser Gly Asp Ile
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